Living is Searching

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Abstract The contribution uses the scientific career of the author to demonstrate one main point: questions are more important than answers. Questions help us to transform information into knowledge and questions are the raw material for scientific explanations. When we are young, we ask questions, later we get accustomed to giving answers. Therefore, the more important part in the life of a scientist are the beginnings. The scientific life of this author began with the childhood question, how plants think, even though they do not have a brain. In the retrospect narrative inspired by this book project, the author finds out that this childhood question has been shaping his entire scientific development, although it adopted different shapes. This inner development is narrated in the context of a professional career that started from a small village in the German mountains over studies in Freiburg and St. Andrews, being confronted with a different mindset during a postdoc in Japan and a road full of obstacles till becoming a full professor in Karlsruhe. Since this chapter is mainly thought for researchers in the early phases of their career, the part of becoming is given in more detail than the part of being. What was important to keep going? What type of mentors one should look for? How to balance professional dedication and private life? The chapter ends with some conclusions as legacy for the next generation to encourage them on their path.

1 PROLOGUE IN VENERATION OF XENOPHANES: Why Questions Are More Important Than Answers

I spent a free, wild, and happy childhood on an ancient castle in a tiny little village in the Allgäu, a mountainous and remote region of South Germany. A long and intricate history had left many remnants that were allowed to wither in dignity and pittoresque decay, hiding numerous secrets and wonders that inspired my vivid imagination. One of our favourite games was "explorers", which meant that we took some candles,

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wooden swords (in case that we would be attacked by rats), and a little crucifix (in case that the attack would come from other worlds) to find our path through the numerous passages that had been driven into the castle mound. With a lot of adrenalin and inspiration, we eventually managed to establish a map of this subterraneous labyrinth and the day arrived, when we had found out everything. I still remember the deep disappointment when I got aware that our expeditions had eliminated all mysteries of the castle.

Many years later, I was a young student of biology in Freiburg then, I was taught by the impressive and stern Hans Mohr, a reputed plant physiologist, that science only advances by falsification of the hypotheses, we had first established with a lot of effort to explain a phenomenon. I did not know about Karl Popper then but needed some time to digest this harsh message and asked one of my other teachers, Rainer Hertel (one of the founder fathers of auxin research), whether there were no alternatives, more positive ways to find scientific truth. He smiled at me through his thick horn glasses that were already outdated those days and asked me back, what I thought, how *Escherichia coli* found the "truth", which in that case would be the same thing as a food source. I remembered, how he had explained to us, that this poor little thing, too small to perceive a chemical gradient at once, because the concentration differences between front and rear of the cell would be overwhelmed by Brownian fluctuations, uses a different approach: swimming straight, as long as the concentration of the attractant increases and searching a new direction by tumbling as soon as a drop in concentration tells that it had swum offtrack. He waited, until the thought could form in my mind and then said—"see, this is, what Popper wanted to say". In the next session, he introduced me to the word by Xenophanes which runs, in the translation by Popper himself (1998):

> The gods did not reveal, from the beginning,
>
> All things to us; but in the course of time,
>
> Through seeking we may learn, and know things better.
>
> But as for certain truth, no man has known it,
>
> Nor will he know it; neither of the gods
>
> Nor yet of all the things of which I speak.
>
> And if by chance he were to utter
>
> The perfect truth, he would himself not know it;
>
> For all is but a woven web of guesses.

I learnt from Rainer Hertel that it is the tumbling, not the straight swimming, that helps *E. coli* to find its path. Or translated to science: it is the question, rather than the answer that helps us to find our way through the "woven web of guesses". I understood—it was exactly, what I had experienced during the explorations of my childhood. The bliss is in searching, not in arriving. This lesson has accompanied

my scientific life since then and still does. This is also the most important lesson, which I try to pass on to my students.

2 Motivations: How I Developed an Interest in Science

HOW I FOUND MY FIRST QUESTION. To find out the own calling can be a challenge, living in a time and a society full of opportunities and distractions. However, we should never forget, that freedom of choice is a privilege bestowed only on a small minority of humankind. Most people on our planet do not enjoy this freedom and must readily accept, what allows them to survive. Even in our privileged societies, individual choice had been the exception, rather than the rule, over centuries.

I feel myself double privileged. First, I was always allowed to have a choice. My parents, whose childhood had been shaped by the war, always told us children that we could not expect much of a material legacy, but that we are free in deciding our professional career and that they would always support us on our path, no matter, what we decided to do. My second privilege was that I did no need to search long for that what I wanted to do. Instead, my decision to become a researcher and to explore the mysteries of living beings, came in a single blow, very clearcut, without any doubts or sways.

I still remember this day very clearly. I was a boy of four years, and the decision was linked with a spruce tree that grew in front of our house. The tree was old, and time had left its traces upon him. This tree was very important to me, and I went there every day. For some reason, I had arrived at the conclusion that a big knothole in its trunk would represent a kind of an ear, and so I talked into the trunkhole about my thoughts, worries, and imaginations. And it would seem to me that the tree listened patiently and sometimes murmured in response. As different as this tree was from me, our relation was somehow personal, I had the impression that there is "someone", not just "something". That particular day, I woke up in the morning from the noise of motor saws, and when I looked out of our kitchen window, I saw, how woodchuckers had already cut down the tree to a short stump. I was too shocked and confused to accept reality. These men that stood around the stump, joking and smoking, had just murdered my tree and they obviously did not even understand, what they had just done. Didn't they see that they had killed "somebody", a living being endowed with the joy of being alive?

This shock made me think and inspired my first scientific question. Apparently, it was not evident for other people that my tree had been "somebody", because it was just too different from us people. Nevertheless, the tree was able to think, I was quite confident about this point. When my father came home from the office for lunch, I asked him "Daddy, how does a tree think?" My father smiled, and told me that trees do not think, because they do not have a brain. What a disappointing answer! I immediately contradicted "I know that they have no brain, but I want to know, how they think, even though they do not have a brain!". As a response, my father just

smiled once more and patted my head. Thus, it was clear, the adults did not know anything. I had to find out for myself!

To become a scientist in a remote village in the Allgäu was not an easy endeavour. There was no internet that would allow me to find answers to my questions, and although I learnt to read very early, the bookshelves of my parents, while containing a lot of interesting stories, did not give any answers to my question, it even seemed that nobody had ever even asked it. So, I started to think by myself.

2.1 What Science is About: To Make Mistakes and then Correct Them, Without Much Ado

The Catholic nuns that were running our *kindergarden* did not appreciate own thinking, nor did they appreciate the many questions, I asked them. I was told to shut my mouth and be quiet. So, I decided, not to go to the *kindergarden* any longer. Every morning, I took my lunchbox, said goodbye to my mom, and pretended that I would go off to the *kindergarden.* Instead, I disappeared into the woods, strolled through the thickings and climbed on my favourite tree, from where I could observe the wildlife. When the bell on the castle tower announced noon, I came home as if returning from the *kindergarden.* It took a year, until my mom found out, by accident. Fortunately, this was a few weeks before school started, a village school, four classes in a room. In the cities, pedagogy was experiencing a thorough turmoil in those days, the old concepts became overthrown in favour of new ideas, such as anti-autoritarian education. But this was still far away and completely unheard in our village. However, my teacher, Fräulein Krug, was a naturally born pedagogic talent, she really loved her children, each one of them and she tried to support everybody on the own path, at the individual pace. She was patiently answering to my questions and when she did not know the answer, she simply told me that she did not know, but then gave me a book and asked me to find it out by myself.

After so many years, I still remember an incident that deeply impressed me. We were talking in the class about the way, how animals survive the winter; some would sleep, some would survive as an egg, others would search in the snow for food. I had observed that the Brimstone Butterfly comes out as soon as the snow starts melting and I asked her, how this butterfly could develop so rapidly from an egg to an adult, if in the snow life activity would be so slow. I proposed that this butterfly might freeze and survive the winter, already being an adult, when the snow melts. My teacher said that this would be certainly wrong, no animal could freeze and survive. When I came home, I looked it up in an old book on insects, which I had found in my parents' bookshelf. And indeed, the Brimstone Butterfly was told to be the only insect that can survive down to −20 °C. Very proudly, I brought the book to my teacher and showed it to her. She read it and then plainly said "Well, Peter, now you have known it better than me, and I was wrong". I was thunderstricken by her response, mainly by the attitude of this response. Although she was an adult and I was only a little boy,

she admitted without any ado that her opinion was mistaken. Only many years later, I understood that she wanted me to learn a lesson, which was much more important than the hibernation practices of the Brimstone Butterfly. I am very grateful for this lesson because this is, what science is about: To make mistakes and then correct them, without much ado.

Soon after, one of my most important wishes came true—for my birthday, I got a little department-store type microscope, which opened me the miracles living in the water drop. I was now looking at anything that came across and learnt a lot. I was especially fascinated by flagellates such as *Euglena* because those were considered the basepoint of life. I was observing and drawing them and was impressed by the complexity of their behaviour. To find special literature on these creatures was really hard but with the help of a dedicated bookstore in the neighbouring town, I succeeded to get three antiquaric monographies from the turn of the century. I devoured those books, even reading foreword and index several times. What I found very striking was the fact that the borderline between plants and animals was quite permissive in these creatures. Thus, plants obviously were not principally different from animals since they derived from the same origins. I wondered whether the nucleus might be something like a cellular brain which would be shared between both life forms, and I squeezed out all information I could from my three monographies but found the information there quite vague. I also felt progressively limited by the lacking resolution of my department-store microscope and went to the local optic store to find out more about real microscopes. The prize, around 3000 DM, was clearly beyond my budget. Fortunately, I just had become fourteen, which meant that I was allowed to search for a vacation job. I worked very hard—first, as a woodchucker in the forest, later, as workhand on construction sites. After two years, I had accumulated the money and proudly went to the store to order an Olympus CHX light microscope. Two weeks later, a car from Freiburg came by and a very astonished salesman handed over a big parcel to me, a schoolboy.

The new equipment advanced my studies a lot. Eventually, I was able to see the details, such as flagella, the nucleus, and even the contractile vacuoles. From a pond behind our village, I got a sample, where I found my first model organism, a zooflagellate called *Peranema trichophorum*, which was well observable, because it did not swim too rapidly and in addition was capable of ameboid movements. I built a simple cultivation chamber, where I could keep this creature for up to several weeks, providing pond water through a cotton thread and from time to time feeding with *Euglena*, which I kept on a decoct from our local cheese (my mother refused to enter my room for weeks). I noticed that *Peranema trichophorum* was somehow capable of recognising its environment. When it encountered an inanimate particle, such as a piece of debris or a sand grain, it retracted and then searched a way around the obstacle. When it met its prey, a cell of *Euglena gracilis*, it protruded a stick-like organ at its front, slat its victim open and devoured it by phagocytosis. When it met a fellow, a deadly battle ensued, which usually ended by the larger cell devouring the smaller. Sometimes, when the cells were similar in size, the battle remained undecided, which attracted additional cells that joined into the fight, which was then

hard to follow. When they separated again a few minutes later, one or two of the cells had disappeared. Apparently, this flagellate displayed cannibalistic manners.

This phenomenon had really caught me—how could it be that such a primitive cell was able to show such complex behaviour? Obviously, the cell was able to sense touch and this sensation must be processed somewhere, integrating additional information, such as being inanimate, being prey, or being a fellow *Peranema* cell. I came back to my old idea of the nucleus as a cell brain—would this be the place, where all these stimuli are processed? How could I find out? I developed the crazy idea that it should be possible to stimulate the cell at different locations with a fine glass needle and measure, how long it would take until it responds by a contraction. To make a fine needle was the easy part of it—I had got Pasteur pipets from our pharmacy and had learnt to draw thin capillaries over a candle flame. But how to handle the touch in a manner precise enough for my experiment. I did not know about micromanipulators at that time and even if I had known, those devices would have been unreachable for me. So, I invented a system of levers using my Märklin metal kit, where I could handle my glass needle with sufficient precision to conduct the experiment. To keep things simple, I decided to do only three settings—touching the rear (intermediate distance to the nucleus), touching the middle (very close to it), or touching the tip (very far from the nucleus) of the cell. After some exercise, I became quite good at it and persuaded my younger brother to sit by me and take the time with a stopwatch. I remember, how excited I was, when I started to plot the times over the three positions and saw a clear increase of reaction time over distance to the nucleus.

In the meantime, two years had elapsed, and I decided to tell my biology teacher about my work. When I showed him the data (including drawings, I had made with ink), he encouraged me to publish this. I had never thought about publication, but then wrote to the editor of *Mikrokosmos*, a traditional light-microscopy journal, describing them my story. They told me, I should write it up and gave me some hints, how to do it. I replied that I would not have access to microphotography, and they agreed that I could document my observations by ink drawings. So, I was writing my first scientific manuscript on my mother's mechanical typewriter and sent it in to *Mikrokosmos*. It took a few months, until I heard back. In addition to the editor, a reviewer had read my paper and suggested that I should come up with an explanation for this cannibalistic behaviour. I was reading in my three monographies and found out that *Peranema trichophorum* was thought to be a distant relative of *Euglena*, which had lost its chloroplasts. I came up with a kybernetic model, where I proposed that there are surface structures that are still conserved, such that under my conditions, where feeding the prey had increased the density of this carnivorous flagellate, also the likelihood of an encounter with a fellow rather than a cell of prey would increase. Due to cannibalism, the number of cells should decrease, and this should also make this behaviour disappear, until a new wave of population growth would bring cannibalism back—an implication of my idea that I was able to confirm experimentally. I even made suggestions, how one might find out about the nature of the inducing factor. The culture filtrate of a dense culture might elicit this behaviour in a culture with only few cells, which would allow to distinguish the mechanism from an alternative,

where the behaviour requires physical interaction to become manifest. My revision was then accepted, and two years later, just right for my 20th birthday, it appeared in print (Nick 1982)—I was already at university then.

3 Work Done: My Personal Scientific Approach

HOW MY FIRST QUESTION SHAPED MY SCIENTIFIC PATH. To move to Freiburg University was a real excitement for me—the town with its a bit more than 10^5 inhabitants was something like Metropolis for the village boy I was in those days. The biology faculty followed a very high standard with respect to teaching quality and dedication. Actually, all prominent figures in research turned out to be great teachers and I learnt a lot, both in terms of science, but also with respect to personality. Dispute was cultivated and it was public, and from the very beginning we were taught to foster doubt and critical thinking, and to question even the most venerable theories. I was grabbing all what I could get, and this extended beyond biology. Greedy for knowledge, I was visiting also courses in ethnology, philosophy, or history. Over eight years in total, I studied Russian literature, attending the legendary course of Svetlana Geier, who re-translated with us the entire work of Dostojevskij. According to her opinion, the Germans had not had the chance to really understand this author, because, so far, he had not been properly translated. I was impressed by her precise language, unfolding the different connotation of a single word, her never-ending struggle for the correct expression, and her big perspective spanning different countries and cultures. Science is strongly dependent on language, and thus, I profited a lot from her course. Our biology curriculum was very broad, so I delved into anything from ecology till biophysics, and probably my teachers needed quite some patience, when I was getting on their nerves after the lecture.

A theme that returned to me repeatedly in different contexts was the question of integrity. What is an entity? Is it more than just the sum of its parts and the interactions between them? Is an ecosystem something which exists only in our minds, or is it there in the real word, does it act in a holistic manner, like an organism? Is a lichen, emerging from the symbiotic interaction between algae and fungi, a new kind of life form, or is it just the combination of the two symbiotic partners? These were the kind of questions, I discussed passionately with my prof in biophysics, Eberhard Schäfer. He was strictly denying that the whole is more than the sum of its parts and so we fought a lot—I listened to his courses, although I did not intend to choose biophysics as subject, but rather was considering going for geobotany (which in Freiburg was shaped by the school of Plant Sociology, dealing with plant associations as shaping element of ecosystems). But for some reason, I was attracted by Eberhard Schäfer's lectures, there was something fascinating about the intellectual challenges to translate biological phenomena into logical elements that could be mathematically addressed and modelled. One day, in the middle of our fight, he stopped suddenly and asked me, whether I would like to do a research project in his lab. I was stunned—it was just out of my scope. But he continued to tell me that they had observed that a maize

seedling, although not able to respond to red light by a phototropic curvature, seemed to *remember* the red light and later would change its response to blue light. And then came the decisive sentence: "Nobody understands it, nothing is known, and you are completely free, how you want to address this." He had got me.

3.1 You Are Completely Free, How You Want to Address This

Already the following Monday I started work in his lab—I learnt to meticulously standardise my system, etiolated maize seedlings. The caryopses had first to be watered for a given time, sown on a particular type of tissue, the air bubbles had to be rolled out with an empty bottle, the caryopses had to be sown equidistantly, embryo up, and the boxes had to stand in a particular region of the light field, which I had to adjust to homogeneity with a variation below 5% (which took me hours), and, eventually, two rounds of selection had to be added to get coleoptiles of exactly the same length. The system had been conceived by Dr. Moritoshi Iino, a Japanese guest scholar, who had driven precision to a stage that even 2° of curvature made a significant difference. The red light to induce the memory effect was extremely weak; when the shutter was open, a beeper signalled to me that the light was on. I was not able to see anything, but my maize seedlings clearly did see something. In the beginning, I worked with a night vision device, which a former Ph.D. student had smuggled in from the military, but later my body knew by heart, where things were in the dark room, which became my home during those days. I was working very hard, combining the different lights in different directions, timings, and fluences. When I stumbled out of the dark room in the evening, I had collected hundreds of data points, and slowly a complex, but clear curve began emerging from the data cloud. Above the little desk, where I was inserting my data points into a graph with a pencil, there was a framed quotation by the famous Karl Hartmann, a pioneer of phytochrome research, who had set up the illumination system ten years earlier from bits and pieces he had acquired from an abandoned burlesque theatre: "If you are not able to generate quantitative data here, you are on the wrong place here."

I started to make hypotheses about the curve that I could infer from my data. Eberhard Schäfer proposed that each cell would act autonomously, measuring the local quantity of red light by the phytochrome system and that the memory could be reduced to just a gradient of red light across the coleoptile. I calculated the consequences and got a curve that looked quite different from my observations. I proposed an alternative idea—that the coleoptile would recognise the direction of the two light qualities in a holistic manner and then *decide*, whether to increase or to decrease the bending. If this was right, I should get the same result if I imposed a certain *relative* gradient of red light, no matter, whether this gradient was established with strong or with weak light. I started to do this experiment, but time was running out, because a few weeks later I was supposed to start a year abroad, at the University of St. Andrews, Scotland. I was now increasing the pace of my experimentation and had to get up very early in the morning to have my maize seedlings done. One day, during

one of the many farewell parties that were celebrated on my behalf, I remembered in the morning at four that I had forgotten to sow my seeds. So, I decided to bring the whole tipsy company to the institute, and we sneaked into our laboratory. They were impressed by the red-light chamber and my discipline in arranging the maize seeds equidistantly. The deepest impression, however, made our discussion room with its central table that was plastered with empty beer bottles, and the blackboards sketches with weird formulae and cartoons, and, last, but not least, our beer-bottle collection that meanwhile comprised all letters of the alphabet. While we were sitting there, drinking, and joking, the night guard passed by, but since such sights were familiar to him, he just shuffled further, without taking any suspicion. My hard work payed off—my data clearly discarded the hypothesis of cell-autonomy and supported my holistic decision model. I still remember the bliss I felt when I plotted the points.

3.2 Scottish Interlude—How Different Parts of a Plant Talk to Each Other

But it was already time to pack my things for one year at St. Andrews University in Scotland. I thought about ways, how to continue my experiments and even took a parcel of the respective maize cultivar with me. However, the parcel did not make it—the custom officer in Victoria Station decided that this would endanger British agriculture and ransacked the caryopses. St. Andrews was a tiny, but romantic town on top of a cliff, and I rapidly merged into the international community there and tried to get what I could, although the Bachelor system with its block courses was not as free as I was used to from Freiburg. I soon started to work on my Bachelor project. Since I was a foreign guest and, thus, a bit outside of the system, I did not have a true mentor taking care of me. This was, what I preferred anyway, I wanted to work freely. Listening to the seminars in the institute, I soon found a topic that attracted my attention, heterophylly in the semi-aquatic plant, *Pogamogeton natans*. This plant produced different leaves, depending on submergence. A Ph.D. student at the Institute of Botany had discovered that in clear Scottish ponds this switch happened already before the leaves reached to the air. Coming from a photobiological group, I started to test the idea that it was the light quality that decided over the transition. Indeed, after a long struggle against algae that tended to overgrow my plants, I was successful to change the leaves by increasing the ratio of far-red light over that of red light, indicative of a phytochrome effect. This led me directly to the next question: the young leaf primordia were generated at the tip of the plant that was already reaching out into the air, but still the leaves that developed from these primordia were of the submersed type. Where was the light actually perceived? On site, in the tip, or in the older leaves? I started to cover up different parts of the plant using aluminium foil and soon found out that it was the older leaves that sensed the light quality, sending a signal to the meristem, where this signal would steer the differentiation of new primordia. I even tried to find out, how fast this signal migrated, but the variability in

my experimental system did not allow to tell this with reasonable resolution. I was writing my first thesis, which was a challenge, because English was not my mother tongue, but my mentors appeared to be quite impressed.

Of course, the year in Scotland was not only filled with science, but I also travelled a lot, joined several of the university clubs. On a sunny spring day, I was taking my lunch in the Russian Club, when the radio announced that Chernenko, the senile last dictator in a row of senile Soviet dictators had died. A new General Secretary was elected the same day, it was March 11, 1985. I listened to the speech of this new leader, whose name was Michail Gorbatschow, and I immediately understood that this was a historic moment. Hard to believe from the perspective of today, where the story that had started then, has inevitably ended. I also delved deeply into the British society, which in some aspect appeared really exotic to me. I also witnessed the conflict around the Miner Strike, which lasted for over a year and really disrupted the society even in this tiny university town. The gap had developed to a degree where students from both sides (coming from quite disparate social backgrounds) frequented separate pubs. As foreigner, I was alien anyway and had the privilege to converse with both sides, which led me to the deep conviction that the ability for compromise is crucial for solving any problem in society.

3.3 How to Sense Direction—Everybody by Himself or all Together?

In summer 1985, I returned to Freiburg and rapidly finished the remaining courses and examinations to start my diploma thesis, again in the Schäfer lab. My story had in the meantime been pursued by a Ph.D. student and was already published. I was not satisfied about this, the holistic behaviour had been ignored in that paper, and I was disappointed. But my prof came up with a new idea: He told me that there was a very old paper by Johannes Buder, who had asked a similar question as me, and recommended me to read that and develop a new idea, which I should pursue then in my diploma thesis. I had to go to the cellar of the well-equipped Freiburg university library to find this paper, which had been published right after World War I. The title "Neue phototropische Fundamentalversuche" (New fundamental experiments on phototropism) was unusual and immediately attracted my attention. The author summarised work he had done during war time under very difficult circumstances, partially he had to work with candles, because the electricity was shut down (Buder 1920). He had designed a very elegant approach using a custom-built light-fibre which allowed him to stimulate a coleoptile of oat (since Darwin's days the favourite model for phototropism research) from inside out, such that the direction of light was opposed to the gradient over the entire coleoptile. If each cell would act autonomously, which was the general concept of that times, the tropistic bending would be defined by light direction. If the coleoptile compared the light perceived in different flanks, i.e., if it acted as an entity, it should bend the other way round

following the gradient and opposing the direction of the light beam. The coleoptiles followed the gradient, not the direction, which meant, they acted as holistic systems. I was turned on. Many years later, I even repeated those experiments and tested the behaviour of microtubules in this context (Nick and Furuya 1996). I was discussing with Eberhard Schäfer, and he convincingly explained to me that such a holistic sensing would not work for gravitropism, because, here, each individual cell must sense the sedimentation of the amyloplasts independently. This discussion brought me to my idea—I guess, he had already conceived this earlier, but he generously allowed me discovering it by myself—what would happen, if a photo- and a gravitropic stimulus would be administered simultaneously? Would the two curvatures just add up by cell-autonomy or would there be deviations indicative of a "holistic decision". He told me that the seedlings, during their bending would experience a counteracting gravitropic stimulus making them straighten up again after some time, which would introduce additional complexity into my already complex experimental design. He adviced me to put the maize seedlings after stimulation on a so-called clinostat, a device rotating the seedlings slowly around their axis, such that any asymmetric gravity during bending would be excluded.

Since I had already been trained in the methodology, my work advanced quickly. I used two set-ups—one, where the two stimuli were acting in parallel and one, where they were opposing each other. For each set-up, I recorded a so called fluence-response curve progressively stimulating the dose (for light such a dose is called a fluence). The opposing set-up was not very interesting to me—the curvature induced by the gravitropic just subtracted neatly from that evoked by the phototropic stimulus alone. This merely additive behaviour supported a cell-autonomy model. The parallel stimulation was much more interesting. Here, for weak stimulation, the angles added up, but if the phototropic stimulus reached its optimum, suddenly something unexpected happened, since the interaction began to turn antagonistic. Apparently, the coleoptile had a limited capacity to process directional signals, and when this capacity was crossed, it responded qualitatively different to the light. This pattern was clearly holistic, as if the coleoptile made *decisions* that were qualitative in nature and not just the sum of their components. To document my readouts, the coleoptiles were glued on a specific tape and then xerocopied, such that the angles could be measured using a custom-built digitiser coupled to a calculator. After my diploma thesis, I had two piles, each of one meter height of xerocopied maize seedlings, which seems pretty pleistocenic from current-day perspective. I even succeeded to mathematically model my data and clearly could discard the original additive interaction model. The manuscript was already written on an electrical typewriter coupled to an antique personal computer. When I gave the first version to my postdoc colleague from Britain for language edit, it came back completely covered with notes in red ink, such that I hardly could find my text. In the iterated version, the red area had already decayed to half and after version four, I could submit and was successful (Nick and Schäfer 1988a).

3.4 Progress by Accident: A Tale About Grey Geese and Maize

Of course, I was quite proud about my first "real" scientific paper resulting from my diploma thesis, but as often in science, the real decision came not from this paper, which even the reviewers found quite complex and hard to digest, but from an accident that happened during this time. As to sustain my living, I had to work in several jobs at the university. I was teaching courses, and, in addition, worked as a lab manager in an analytical company processing blood and urine samples from patients. This company was around one hour by bike from Freiburg and so, I had to bike a lot those days under a very frosty November moon. One evening, after a long day of research work, teaching, and work in the company, I cycled home and suddenly remembered that I had forgotten my experiment launched in the morning. Since it was clear that I could discard those data anyway; and tired and hungry as I was, I decided, to go home and let the seedlings be seedlings and the clinostat turn around. The next morning, I went to the lab to dismantle the experiment and found to my surprise that my seedlings had bent on and on all night long, assuming the shape of pigtails. I was struck by their curious look, but then, I started to think: If a light pulse of 30 s was sufficient to cause an everlasting bending, this meant that the seedling, by this first stimulus, had assumed a stable asymmetry across its axis.

I felt reminded of the little grey geese of Noble Laureate Konrad Lorentz, who had discovered that these little creatures, while hatching, would accept any moving object that came across their sight, as mother for the rest of their life. The impressive proof for Lorentz' "imprinting theory" were the geese that followed him everywhere, no matter, whether he was taking a swim in the lake behind the institute, or whether he was entering his lab. Were my maize seedlings "imprinted" in a similar way by the first light pulse they encountered, when they "hatched" from their caryopses? This idea already led to the next experiment. If there was "imprinting", it should remain stable against the temptations of subsequent stimuli coming from a different direction. I started to do the experiment immediately, and was disappointed: the second, counter-directed, stimulus overran the effect of the first "imprinting" stimulus completely. Again, I got pigtails that curved the whole night, but now in direction of the counter stimulus, as if they had completely forgotten about the first light pulse. I tried to digest my disappointment and wondered, whether it might take some time, until the "imprinting" became stable, like the human mind that also needs around 20 min to memorise something in a stable manner. Thus, I increased the time interval between the first and the second stimulus and probed by prolonged rotation on the clinostat, in which direction the bending would develop. Up to 90 min, the second stimulus won completely over the first, but if I allowed the first stimulus more time to exert its effect, something strange happened: the coleoptile briefly started to follow the second stimulus, but then suddenly stopped and bent in the direction imposed by the first stimulus. After a few hours not any trace of the second stimulus was detectable. Thus, the coleoptile had developed a spatial *memory*, and this spatial *memory* was stable even through times, when it was not manifest as a curvature. The coleoptile

took a decision, which was all-or-none. In fact, when the challenging counter-pulse was administered just at the time, when the spatial memory was fixed, the population became very noisy—some already bent very strongly in the direction of the first pulse, some still bent very strongly in the direction of the second pulse, and a few could not decide and remained straight.

When I was writing up my second paper on this "spatial memory" (Nick and Schäfer 1988b), I suddenly understood that, unconsciously, I had returned to my first question from childhood. "How do plants think, even though they do not have a brain". Although this paper remained purely phenomenological, without a single molecule being addressed, it has remained important to me since, because it was a kind of enlightening experience, where my future path emerged from the mist. With this point, my "scientific childhood" had inevitably ended, and I felt that I had found my vocation as scientist.

4 Science Today and Tomorrow

FINDING ANSWERS AND NEW QUESTIONS. My discovery induced me to ask further: When a short light pulse of a few seconds was able to imprint a spatial memory that was stable over several days, there must be some structural correlate on the cellular level. In the human brain, memory is encoded by the mutual connections of the neurons. The cellular correlate of these connections are ramifications that are kept in shape by long and stable bundles of microtubules. While reading about these fascinating organelles, I learnt with astonishment that they had not been discovered neither in animal cells, nor in the context of the division spindle, as I had naïvely assumed. Actually, a biophysicist, Paul Green, had predicted them in the year of my birth due to considerations on expansion growth in plant cells (Green 1962), and one year later, two cell biologists, Ledbetter and Porter (1963), had looked for these predicted structures and discovered these "micro-tubules" underneath the plasma membrane of plant cells by transmission electron microscopy. Using the same technique, the team of Paul Green was able to show that reorientation of these microtubules by ethylene can induce a tilt of cell expansion from elongation to lateral thickening (Lang et al. 1982), because microtubules serve as guiding tracks for the movement of cellulose synthase complexes that will lay down the cellulose fibres in parallel to the microtubules and, thus, define the direction in which the cell can expand. I wondered whether these reoriented microtubules might be the cellular correlate of my spatial memory. A methodological innovation that became accessible just at that time also for plant tissues, immunofluorescence (Lloyd 1987), helped me to address this.

The idea to address "spatial memory" in terms of microtubules was not only fascinating for me, but also appealed to Eberhard Schäfer. He proposed me to apply for a Ph.D. fellowship from the German Scholarship Foundation. They had selected me already, when I was still at school, and they had also funded the tuition fees during my year in Scotland. I applied and I got the fellowship, so that I could start

with my Ph.D. straightaway without the need to keep myself alive by side jobs. My path was now spread out clearly in front of my eyes. I learnt how to label microtubules by immunofluorescence, after carefully peeling off the epidermis, since this tissue was known to control the elongation of the entire coleoptile by limiting its extensibility. In fact, microtubules underwent a re-orientation during phototropism. In the dark, they were oriented perpendicular with the cell axis. In the illuminated flank of the coleoptile, they realigned parallel to the cell axis, while they maintained their transverse orientation in the shaded flank. A similar reorientation could be evoked by decapitation of the coleoptiles, such that the cells became depleted from the growth hormone auxin. Conversely, by addition of exogenous auxin, microtubules could be turned back to their original transverse orientation. I followed the time courses of these processes and arrived at a model, able to explain phototropic bending: a lateral blue light pulse caused a shift of auxin from the lighted to the shaded flank, the cells in the lighted flank would become depleted from auxin, this would induce reorientation of microtubules into longitudinal arrays, such that cell elongation would not be any longer sustained. In contrast, in the shaded side, growth would proceed unrestrained, and the resulting gradient of growth would lead to the bending. To strengthen my point further, I could also show that this mechanism worked for gravitropism as well. The resulting paper (Nick et al. 1990) was widely read and still is my paper with the largest number of quotations.

However, my original motivation was not to explain phototropic bending, and I thought anyway that my explanation was too simple to be entirely true. The cell has numerous tools to rapidly control growth, for instance by activating ion channels culminating in changed flexibility of the cell wall, or by breaking down starch, such that the turgor pressure is increased. Why should the cell go for a much slower mechanism, such as realigning microtubules in a new direction? Such architectural changes would rather be meaningful to obtain stable changes. My original fascination for microtubules derived from directional memory and so I asked what happened to the gradient of microtubule orientation after the bent coleoptile had straightened again. If microtubules were in charge of the instantaneous growth response, this gradient should have disappeared. I tested my implication and was happy to find it wrong. The microtubule gradient persisted, no matter that the bending had already disappeared long ago (Fig. 1). In other words: microtubules behaved in exactly the same way as spatial memory was predicted to behave. Using complex combinations of stimuli, clinostat treatments, and waiting times, I could corrobate this parallelism and show, how microtubule reorientation developed in response to a directing blue light pulse and acquired stability at the same time, when the spatial memory became fixed. This memory effect was unique for blue light and could not be mimicked by a mere gradient of auxin, even though this gradient induced similar curvatures (Nick and Schäfer 1994). However, I was able to cancel the memory by cytochalasin D, a compound eliminating actin filaments, the second important player of the plant cytoskeleton.

My phenomenological approach had reached a stage, where the complexity of my experiments made it progressively difficult for others to follow my reasoning. I remember the comment of one anonymous reviewer of a paper stating that he

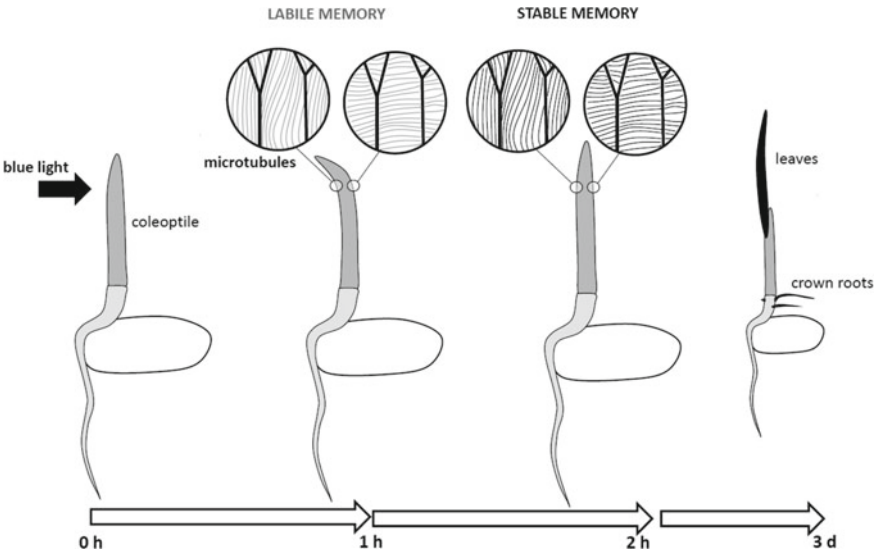

Fig. 1 Spatial memory is embodied as a stable gradient of microtubule orientation. When a maize coleoptile is stimulated by lateral blue light, it will bend and microtubules at the lighted flank will assume a longitudinal orientation, while they remain transverse in the shaded flank. This gradient is first labile, because it can be inverted by a light pulse from the opposite direction. However, 2 h after the inducing light pulse, the microtubule orientation is fixed, even though the bending has disappeared. A few days later, this memory guides the emergence of crown roots

found this great science, but very hard to follow and that he had difficulties even to understand my questions, not to speak about my answers… Anyway, the time of my Ph.D. had come to an end, which was also true for my scholarship. It became clear to me that I would need to search for molecules to understand, how directional memory would guide microtubules.

4.1 Fighting in the West, Journey to the East

Around this time, it was the last year of my Ph.D., a Japanese professor, Masaki Furuya, paid a visit to our institute and listened attentively to my account on my experiments and ideas. He was asking very stimulating questions and seemed to like my work. Moreover, he appeared to be a nice and generous person. When we were finished, he suddenly asked me, whether I would like to come to his lab in Japan. He told me that the Japanese government had launched a new policy to attract foreign scientists to Japan in order to stimulate scientific creativity. As part of this policy, they also offered prestigious scholarships. Since it was clear to me that a scientist needs to see the world to get confronted with other ideas, I was already pondering a postdoc. However, to go to the US, which in those days was the usual way for a

young scientist from Germany, was not really appealing to me, because the US was certainly not different enough for my taste. To go to Japan and delve into a culture and way of thinking that was far from mine, appeared much more attractive. I did not think long and answered that I would come.

I designed a project to elucidate the biochemical changes underlying the blue-light induced spatial memory and sketched down some ideas, how candidates could be identified and validated. To my pleasant surprise, the project went through smoothly, and I would start in Tokyo at the start of the next financial year, which in Japan begins April 1.

The journey to the East belongs to the most impressive memories of my life. I did not go for the easy way taking an airplane, although the Japanese government offered to pay for everything. Instead, I decided to use the Transsiberian Express to Wladiwostok, from where I hoped to catch a boat to Yokohama. It was autumn 1989, the Iron Curtain that had separated Europe for all my life, had collapsed without a single shot. I was in the middle of events—in October 1989, I had travelled as translator with a delegation from my hometown, Freiburg, to Lviv in the Ukraine to negotiate and sign a city friendship. This friendship is still active and more important than ever in those days of war, because ordinary citizens organise transport of food, medical goods, and important commodities, such as emergency generators, from Freiburg to Lviv and on the way back take women and children to Freiburg. Who could imagine this in those days? Just the day after our arrival in Lviv, the Berlin Wall fell, and everybody was tantalised. In the weeks to follow, one country after the other threw off the chains of dictatorship. In November, I was in Budapest to get the ticket for the Transsiberian Express on the grey market. For a Westerner, it was still not possible to do this officially, but Hungary, which in those days was at the forefront of fighting for democracy, just ignored the old rules, and so I could get both visum and ticket for a few DM. In January, I defended my Ph.D., *Versuch über Tropismus, Querpolarität und Mikrotubuli* (Attempt on Tropism, Transverse Polarity, and Microtubules), which raised some turmoil, because I had started off with Goethe's famous poem on the *Ginkgo* tree from the West-Eastern Diwan (Goethe 1819). This poem deals with polarity and allowed me to develop my concept. I was accused of mixing poetry and science and one professor even threatened me to make the thesis been turned down, if I did not withdraw and rewrite it. I refused because I found Goethe's description of polarity exactly to the point. As a consequence of my refusal, I had to face a very harsh review process, where additional external reviewers were asked. One of them even died during reading my thesis, as I learnt years later. It took several months, until the faculty arrived at the conclusion that this thesis was *summa cum laude* (excellent), I was already a postdoc then in Japan and waited urgently for my Ph.D. certificate. Nevertheless, looking back, I still would act the same way, although it had brought me into trouble.

So, I left Germany, on an icy winter day early in 1990, travelling through the dramatically changing countries of Eastern Europe and the incredible widths of a starving, but free, Russia. On the way, it was somewhere in Western Siberia, I learnt that there would not be any ship from Wladiwostok before May, because the sea was frozen. Fortunately, I could bribe a railway agent to change my ticket for Beijing,

where I arrived in the dawn of a cold day in March, after ten days without food (the train restaurant had closed soon, because the cook sold the food to the local population during the rare stops in Siberia). The train entered Beijing, moving very slowly through the baracks along the rails, and thousands of people lined our path, conducting their morning Tai Chi, a sight as surrealistic as from a dream. China had been less lucky, the Tiananmen upheaval in June 1989 had been quenched in blood, and on all my ways through Beijing I was followed by secret agents that did not even try to pretend that they were civilians. Still, I was impressed by the hospitality and curiosity of the people, and really enjoyed floating in the streams of thousands of bicycles that were moving as smoothly as the Tai Chi practitioners I had seen the day of my arrival. I heard rumours about a ship from Shanghai to Kobe and managed to organise a train ticket—three days on a so-called hard seater (which meant a wooden bench). The ship really existed, and it was not even difficult to get a ticket. Thus, on the last day of March, just in time, I reached Tokyo successfully ready to start my new life as a postdoc.

4.2 Learn About Yourself, by Understanding the Other

The lab of Prof. Dr. Masaki Furuya was among the cutting-edge groups in the field of plant photobiology, mainly phytochrome. Furuya-*sensei* (literally "the one, who lived before me"), as I called him, following the Japanese habit, was a very energetic person. At that stage, he had already retired twice, first after finishing his professorship at Tokyo University, then, after he had helped to build up the National Institute for Basic Biology in Okazaki. Now, he was a central figure in the Frontier Research Programme at the RIKEN Institute in Wako-shi, just at the city border of Tokyo. The Japanese government had decided that creativity should be boosted by attracting foreign scientists and adopted a policy of *kokusaika* (internationalisation). I was one of the first people profiting from this new policy, but since Japanese do things very thoroughly, when I left two years later, there were already more than 200 foreign scientists in the institute. As I was not working primarily on photoreceptors, I did not belong to the core of the group. Moreover, I brought my own money, which gave me a certain independence. I started off to do biochemistry, looking for microtubule-associated proteins that were responsive to light. Furuya-*sensei* was a demanding, but also a very supportive boss. When I needed anything, he would move all his levers such that I could meet the respective person. So, I learnt to use a very efficient affinity method to purify plant tubulin, which had been developed by an extremely modest, but skillful biochemist, Mizuno-san. This method is still of use in my lab to our days. Furuya-*sensei* had spent ten years as postdoc in the US and knew in person almost everybody who was important in plant biology those days. In addition, he invited many scientists to visit and discuss. So, I learnt a lot during that time, polished my discursive skills, and also profited from the analytical education I had obtained in Freiburg.

Of course, I also wanted to see the country and learn something about its culture. The fellowship funded very generously language courses in Japanese, and so I took four hours a week and got up every morning at five to learn *kanji*, the Japanese characters. Although I never reached to a stage, where I could read and enjoy Japanese belletristics, I came along quite well and also travelled quite a bit. This was not so easy, because the fellowship did not foresee any vacation, but I had an implicit agreement with Furuya-*sensei*. When I wanted to ask for a leave, I just put a manuscript for publication on his desk and asked for a "business trip". Everybody knew that this "business" did not exist, especially, when, after one year, I was travelling through China, Mongolia, and Siberia, but as long as the formalities were maintained, it was fine. During those two years, I absorbed this completely different culture and way of thinking and was astonished that, by doing so, I did not only learn a lot about Japan, but also about Europe. Never before in my life I had to explain my way of thinking. Now, I had to and found out that my way of thinking was not just "human in general" as I had assumed before in my naïvety, but that it was also specifically "European".

After my first year, three events shaped my path:

4.3 A Fancy Microscope Allows to Ask a Fancy Question

Furuya-*sensei* entertained a long-lasting cooperation with Hitachi, and they had built for him the large Okazaki spectrograph, a unique device for photobiological experiments. It was basically a gigantic light source generating the entire spectrum emanating in a huge circle. Basically, each nanometre was expanded to around 10 cm and the light was strong enough to elicit biological responses. Now, Furuya-*sensei* had convinced them to build a microscope, which would allow for microbeam irradiation, combined with an infrared optics, such that one could search the target cell without the need for visible light (which would activate biological responses). This fancy toy was just ready and now waiting for applications. I once had the chance to talk to the CEO of Hitachi at occasion of a dinner, organised by Furuya-*sensei* in gratitude, and I asked this leading manager, what the benefit was for them in building such devices as the spectrograph or the infrared microbeam irradiation microscope. The answer of the Hitachi manager was surprising for me—they would not get any benefit for the moment, but the technological challenges they had to solve in order to meet Furuya-*sensei*'s demands might help them in 50 years from now. I often remember this answer, when I read about another example of short-sighted economical leaders in the West.

I did not have to think long to come up with an application: during my work on the spatial memory in Freiburg, I had understood that organisms have to make decisions that are qualitative. Whether my coleoptile followed the first, imprinting stimulus, or whether it decided to follow the opposing, new stimulus, is a decision as fundamental as a pregnancy. It is all or none, there is no room for any graduality. This decision not only guides short-term bending, but will also define, on which side the root system is laid down several days later (Fig. 1), as I had already observed at

that time, although published it only after my return to Europe (Nick 1997). Such qualitative decisions require some kind of signal amplification, which means that, at the transition point, the population will be very noisy, because some individuals decide for the left, while the others decide for the right. This was exactly, what I had found and what inspired my interest into threshold phenomena in biology.

I did not need to search for long. Hans Mohr, the founder of Freiburg biology, was working on the effect of light on plant development, and his favourite model case was the induction of anthocyanin in cotyledons of White Mustard (*Sinapis alba*). A pulse of red light activated the photoreceptor phytochrome, leading to the accumulation of the red pigment anthocyanin (Fig. 2a). The Mohr lab had standardised this system to such a precision that it was even possible to relate the amount of extracted anthocyanin to the percentage of active phytochrome (Fig. 2c). The degree of precision was impressive. One of my student jobs consisted in preparing the seeds for these experiments. After they had been selected for size and uniformity, the final test, they had to pass, was to let them roll on an inclined board—only those that rolled straight without deviation, were allowed to enter the experiment. The Mohr lab had shown that the readout showed a threshold, with anthocyanin forming only if activated phytochrome crossed a certain threshold. I wondered whether this model might be a good candidate for Furuya-*sensei*'s fancy microscope and proposed to address this phenomenon on the single cell level, since all the experiments before had used irradiation of the cotyledon as a whole, such that potential interactions between different cells would remain unnoted.

Furuya-*sensei* liked the idea and not only gave green light to me, but also invited (and funded) a research visit of Eberhard Schäfer, who was interested as well.

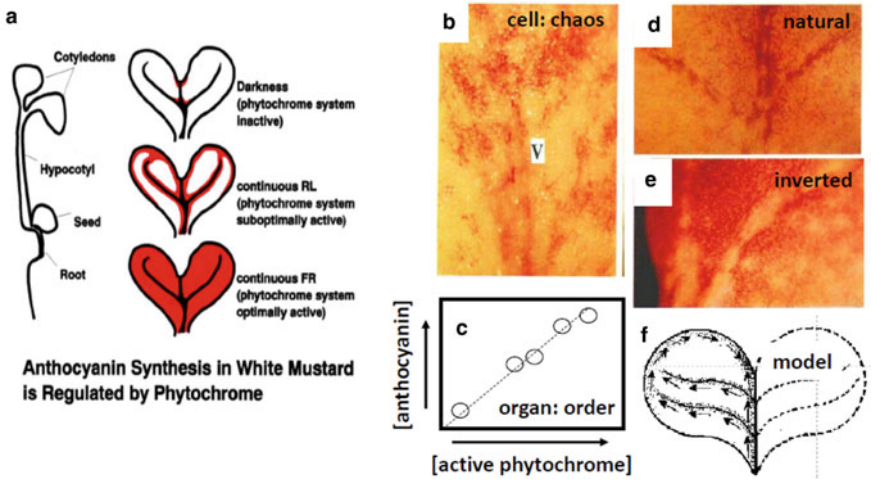

Fig. 2 The anthocyanin pattern in the model plant White Mustard (*Sinapis alba*) emerges from chaotic cells talking to each other by a transportable signal and, thus, creating together an orderly pattern of the entire organ. Summary of the microirradiation experiments (Nick et al. 1993)

What followed, were several weeks in green safelight (which is not perceived by phytochrome) at the microscope. In total, I conducted more than 2500 microbeam irradiations and analysed the resulting anthocyanin pattern. The results were astonishing. I observed that the individual cells followed an all-or-none pattern—a given cell either decided to produce the full set of anthocyanin and turned red, or it decided not to respond at all and stay white. Even neighbouring cells behaved differently, producing a very stochastic readout (Fig. 2b). This was a shocking contrast to the high precision that had been found in the Mohr lab by extracting the entire cotyledon. When I irradiated individual cells, I observed in most cases that only the irradiated spot activated anthocyanin, indicating that the cells responded to the local intensity of light, they perceived. However, if I directed the beam on the leaf margin or the leaf vein, where cells were more elongated, the result suddenly turned global. Interestingly, this global effect was in some cases stimulating, in other cases it was repressive. I was even able to invert the natural pattern, where veins and leaf margin were coloured, while the intercostal cells remained white. By stimulation of specific spots, I could generate leaves that were a mirror image—now veins and margins were white, while the intercostal cells turned red (Fig. 2d, e), breaking a paradigm announced by Hans Mohr that patterns are inherited, but just their expression would depend on the environment.

After all, I could explain the complex patterns by a model, where a factor required for anthocyanin was transported along the leaf veins from the leaf base to the leaf margin (Fig. 2f). Those cells, where phytochrome had been activated, attracted this factor, such that other cells were depleted from it (leading to the observed repression). The individual cell responded all-or-none, but the cotyledon as an entity responded in a gradual fashion by integrating the individual cell responses via systemic signals. The fact that even neighbouring cells differed strongly in their threshold led me to propose that this would allow to reconcile high sensitivity (requiring efficient amplification leading to an all-or-none output) with the need to still adequately respond when strong signals differ in intensity. Thus, cellular noise was not something, the plant tolerated, it was something that was actively maintained to serve the needs of plants that have to adapt to signals that often differ by several orders of magnitude. Furuya-*sensei* was quite pleased that this story (Nick et al. 1993) ended up in a prestigious journal, and it became clear that he was looking for ways how to support my path into science.

4.4 If You Are in a Conflict—Listen to Your Guts

I was able to meet in person many people, which I had previously known only from literature. As I learnt later, Furuya-*sensei* had also discussed with them about possibilities for my future career. One day, the famous and powerful Nam-Hai Chua came for a visit. He was heading two labs, one at the Rockefeller University in New York, the other in Singapore. I was impressed by his sharp mind and straight questions, but I also felt a bit intimidated by the air of extreme ambition he emanated.

He seemed to be interested in my anthocyanin story and asked very stimulating questions. Later in the evening, I was just sitting on a sofa, chatting over a beer with my lab mates, he suddenly joined and asked me straightaway, whether I would like to guide his lab in Singapore. From surprise, I almost fell from the sofa. He explained to me that he had assembled there many laborious researchers from China that were quite skilful, but that the lab lacked conceptual guidance. The position would be for five years and if I wished, I could stay forever. Although this offer was almost immorally attractive for a young postdoc, who did not know, on what to live after the fellowship ended a year later, I felt somehow uneasy and asked for a night to sleep over. He conceded this but told me that I should agree the next morning, he would not be the person to ask twice.

I did not sleep very well that night, but close to dawn, I dozed off. Early in the morning, I was suddenly awake and felt very clearly that I should decline the offer, although I could not give any rationale for my decision. After the breakfast, I told Nam-Hai Chua that I would not take the position. He was honestly surprised but kept composure. To his honour I have to say that he never showed any resentment on my behalf afterwards. I felt a bit embarrassed in front of Furuya-*sensei*, who had probably arranged this proposal in the backstage. He was astonished as well, but when I explained him that my gut-feeling had clearly told me that it would not work, he understood immediately and said something unexpected. This offer had been certainly a great chance, he said, but to his opinion my vocation was to act in the science of my own culture, and not elsewhere. After that I did not need to wait for long to get a second chance. Already a few weeks later, a French lady came for a visit—Anne-Marie Lambert from Strasbourg, I knew her name from pioneering work on plant tubulin and wonderful movies she had generated from microinjecting fluorescently labelled tubulin into plant cells. It turned out that she had been a friend of the Furuya-family since many years and Furuya-*sensei* used all his charms to make her stay unforgettable, including even a visit in the old Shogun capital Nikkô with a night in the garden house of the former emperor. At the occasion of a banquet in a traditional restaurant, where the Tokugawa Shogun had feasted three centuries earlier, Furuya-*sensei* came up with the information of a brand-new funding programme by the Human Frontier Science Organisation Fellowship that fostered transcontinental interactions, and, before the meal ended, the plan was born that I should apply for a postdoc stay in Strasbourg and work on microtubule-associated proteins. I was as surprised about this turn of event (as I had been over Nam-Hai Chua's offer before), but this time, my gut-feeling was positive, and I agreed immediately.

4.5 If You Get a Chance, Grip It—Think Afterwards!

Half of my time in Japan had already passed when, one day, Furuya-*sensei* approached me with a new request: he told me that the Ministry of Agriculture, to which he was an advicer, entertained a so-called *Gamma-Fierudo* (the Japanese pronounciation for Gamma-Field) around 100 km North of Tokyo. There, they would

generate mutant collections of many crop plants, including rice. Everybody now would go for mutants in *Arabidopsis* and these mutants had been useful to understand the function of photoreceptors. Would this not be a great option for doing similar things in rice, for instance, searching for a phytochrome mutant? As scientists, we were funded by the taxpayer, he continued, rice as most important staple crop in the world would certainly be more relevant than *Arabidopsis.* Actually, I was already rather booked with my other projects, but I noticed that Furuya-*sensei* insisted as he never did before, because he came up with the same proposal five times during subsequent days, and I understood that this was the Japanese way of giving an order. I proposed that I would be willing to do that, if, in addition for searching phytochrome mutants, I would be able to search for cytoskeletal mutants. Of course, I did not utter this so bluntly, but in the Japanese style, stating that it would be a great idea to search for phytochrome mutants and at the same time search for mutants affected in the growth response to phytochrome, such as microtubule mutants to get a comprehensive view on the signalling and responses to phytochrome. I noted that, for a heartbeat, he looked at me with a somehow examining look, but then he immediately seemed delighted and told me, he would call them immediately. I also noticed a kind of pride, as if his student had mastered some of his implicit lessons.

Already the next day, I got a call from a Japanese researcher, who excused continuously that he was not able to speak English, and suggested me, whether I might kindly consider paying a visit to their humble institution (which was funny, because actually it was a favour I obtained from their side). The visit in the *Gamma-Fierudo* was a bit eery—my train stopped in a tiny country-side station, and the very shy, but kind researcher, Yamane-*san*, picked me up with the car. We were driving through a lonely forest, while I spotted tumours at several trees and saw blackbirds with marbled white plumage. The *Gamma-Fierudo* was a gigantic circle surrounded by a huge dam. A really big cobalt bomb in the centre irradiated anything around for twenty hours a day, and a siren announced, when it was moving underground for four hours, such that busy gardeners could run out from the shelters to do the cultivation work. I learnt from *Yamane*-san, how they had generated the mutant population of a rice variety called Nihonmasari, and he proudly showed me his trick, how he was cultivating the seedlings on a floating mesh to simulate the conditions of a rice paddy (this simple, but ingenious method, which was not published, turned out to be useful in our lab for the decades to come—hereby, I pay tribute to its inventor).

I returned from the trip and, indeed, a few days later, several parcels arrived with more than 6600 mutant lines, and I started my work. First, I calibrated the system using the *Nihonmasari* wild type and learnt a lot about the physiology of rice. My Freiburg legacy has taught me that a thorough knowledge of your system is the key to success. Afterwards, I was conducting several screens, using Yamane-*san*'s floating-mesh method, searching for mutants with elevated resistance to different antimicrotubular drugs, mutants with altered gravitropic behaviour, and, of course, also mutants where the response to red light, inducing phytochrome, was altered. I was working very hard, spent weeks in the darkroom, and I squeezed out all what was possible from this collection till the last caryopse. Some of these mutants are still in use in my lab even nowadays, so this work was well invested. However, it was difficult

to propagate the selected plants in that institute because there were no greenhouses, not to speak about rice paddies. The only facility was a large phytochamber, where my Japanese colleagues raised some tobacco plants under continuous light. I spent hours every day to get my mutants growing, which was not an easy job. I was glad to see them thrive after all, but unfortunately, they did not intend to flower. My time in Japan was coming to an end, it was already January, and my plants were almost taller than me, but did not show any sign of flower development. In my desperation, I phoned to Yamane-*san* and learnt that this variety of rice, coming from Honshû, the main island of Japan, was a short-day plant. So, since it was not possible to set the chamber on a short-day regime, I had to go every afternoon at four and bring my plants to bed, waking them up the next morning at eight. Indeed, end of February, I noticed the urgently desired flag leaves announcing flowering, and end of March, I could harvest the seeds. Only one of my mutants did not set seeds, although it had flowered. It was a mutant, found in the screen for a lacking phytochrome response, which produced very long leaves that were creeping on the ground, which inspired me to baptise it as *hebiba* (Japanese for 'snake-leaf'). Apparently, this mutant was male sterile. Fortunately, I had kept not only the homozygous mutants (the mutation is recessive), but also two of the heterozygotes, and one day before my departure, I harvested five seeds from them. At this time, I still did not know, where I would be after my arrival in Europe, because the outcome of my application for the Human Frontier Scicnce Programme had not yet arrived. Following my principles, I planned to return to Europe without the use of airplanes. Anyway, my next stay (if it got funded), would not start before June, such that I was left with a gap of three months. The other mutants had been sent already to the address of my former institute in Freiburg, and I decided to take the precious five seeds of *hebiba* on my body, in a little plastic bag, which I kept inside my shoe.

4.6 Journey to the West, It Is Good to Go Out, It Is Good to Come Home

And so, the last day of March 1992, I left Japan, on the ferryboat to South Korea, not knowing, how and even whether I would continue my scientific career after my arrival in Europe. When I was on the gangway, I was called out and a clerk handed over a fax to me. It was the message from the Human Frontier Science Programme congratulating me that I had got the fellowship. The fax had arrived early morning in the institute. How Furuya-*sensei* managed to find out about my whereabouts and forward the fax, I still do not know, but of course this news filled me with great relief. The journey was full of adventures and impressions—after two weeks in South Korea, a country that just had returned to democracy and was full of contrasts and change, I took a boat to Qingdao in China. The two countries still did not entertain diplomatic relations at that time, and therefore this boat officially did not even exist, but it was already full of South Korean businessmen. In China, I managed to get a train ticket

to Mongolia on the black market. I had to go a Roast Duck Restaurant, where I was guided into a kitchen in the back, already wondering, whether this endeavour would have a happy end. It did, and so I ended up in a train filled with Mongolian smugglers that had filled all the cabins with suitcases and bags. Since a Mongolian visum was very expensive and my Mongolian friends had adviced me not to do it the official way, because it would take months, I arrived in the town of Er-Lian in the Gobi Desert and persuaded the obviously helpless custom officer that he should know that as a German citizen I would no longer require a visum, because due to the re-unification, Mongolia and Germany were now brother nations. He seemed sceptical, but due to a sandstorm he obviously had no way to verify my fairytale and after four hours he returned my passport with a stamp. The following weeks passed in a similar manner, the Soviet Union had ceased to exist, now there were many new borders with new rules that nobody knew, and I smuggled my seeds in my shoe undetected till the border between the Ukraine and Hungary behind Ushgorod. The Ukrainian custom officer seemed determined to upgrade his meagre salary, because he searched all my luggage and even my clothes, but to no avail. At the end, frustrated, he commanded me to take off my shoes and found the bag with the seeds. I explained him that this is for science, but he did not seem impressed. So, after all, I asked him, how much, and after some bargaining, he accepted fifty US $. When I look at the value these five seeds had brought to my science later, this bribe was well invested.

Soon later, it was a warm and humid summer day, I entered the *Institut de Biologie Moleculaire des Plantes* in Strasbourg, and joined the lab of Anne-Marie Lambert. With exception of a Ph.D. student, who defended those days, I was the only male—in the institute, the lab ran under the name "The Lambert Girls"—and I was also the only non-French. Despite this double minority statues, I merged in quickly and learnt a lot about biochemistry. The molecular work was complemented every Friday by group meetings, where everybody was supposed to bring a product of own culinaric activity, which allowed me to considerably expand my cooking skills (when I left the lab two years later, I got as farewell as gift a great book "La Nature dans l'assiette" (Nature on the Plate), a collection of vegetarian dishes arranged through the seasons of the year, which is still a source of inspiration for me. In addition to biochemistry, both in scientific and social contexts, I learnt quite a bit about tissue culture, and I applied these new elements to the questions, I had brought from Japan.

4.7 Sometimes, Nature Does not Want to Reveal Its Secrets

Since microtubules can reorient in response to light, there must be associated proteins that interact differently with microtubules, depending on signals from the environment, and this interaction is the core of the fascinating ability of plants to adjust to the conditions by changing their shape. My host lab had developed antibodies against microtubule-associated proteins from neural tissue that recognised proteins from plants, and they also had developed approaches to purify such proteins through their interaction with microtubules. I got the chance to apply these tools and approaches

to coleoptiles from maize and rice and discovered two proteins that were cross-reacting with the antibody and bound to microtubules but appeared and disappeared depending on the status of the plant photoreceptor phytochrome (Nick et al. 1995). I worked then more than a year to purify the two proteins, in order to obtain peptide fragments that would, in the future, allow to clone out the respective genes. For the protein that prevailed in non-growing cells, this approach was successful, and I identified Heat-Shock Protein 90 as microtubule-associated protein (Petrašek et al. 1998; Freudenreich and Nick 1998). The second protein, much more interesting for me, since it was activated when microtubules reoriented into transverse orientation, was purified as well, but when it was sent to our cooperation partners that did the sequencing, apparently some accident happened, and most of the sample got lost, such that I remained only with very few fragments that did not lead to any known protein (the coverage of databases was not comparable to that what we have nowadays). There was no time left to relaunch this purification, and although I have later tried several times to catch it by other approaches, this protein has remained a phantom that lured me to interesting places since, but till now preferred to stay elusive. Maybe, I will catch one day, but maybe, I should accept that, sometimes, Nature does not want to reveal its secrets.

4.8 The Path to Independence Leads Through a Valley of Uncertainty

I had now, over the years, walked on a path coming from the realm of phenomena (spatial memory), over cellular mechanisms (microtubules) to the world of molecules (microtubule-associated proteins). Should I continue along these lines, analyse further, and try to reach towards the level of genes, or should I rather go for a synthetic approach and try to integrate the lower system levels into an understanding of the entire organism? The rise of molecular genetics as dominating approach was already felt those days. The use of *Arabidopsis thaliana* as model organism, the genome project for this organism, and T-DNA mutant collections that allowed for reverse genetics was attractive and became soon the main flow in the plant sciences. Should I join this flow, which also would make it much easier to find a position in a university? Although I was quite impressed about the work of the Gerhard Jürges group on embryogenesis mutants in *Arabidopsis thaliana*, my gut feeling told me that this was not my path.

At this time, I not only crossed a crucial point of my scientific path, also my private life changed fundamentally. Our daughter was born, which made me aware, how happy and blessed my life was. Of course, it was a challenge as well, the following three years, I learnt that a man can keep going even with little sleep. It was also clear that the more adventurous period of my life would need now to become steadier, since I was bearing the responsibility for a young family. In Germany, it is very hard to get a permanent position in academia. Actually, a professor position is

almost the only way. To be able to apply, one needs a degree beyond the Ph.D. This so-called habilitation is basically a second book, along with experience in teaching. I applied for a habilitation fellowship to return to Freiburg, where my family lived already (I commuted every day, which meant to get up at five in the morning, which at that time was anyway the preferred activity time of our daughter). I also started teaching, first at the trinational École Supérieure de Biotechnologie Strasbourg, later at Freiburg University. I liked teaching and still do, my repertory was broad, from evolution, over plant anatomy, till modern methods, physiology, cell biology and biotechnology, and I profited from the memory of my excellent teachers I could enjoy as a student. My application for the fellowship was successful and I even got a position for a Ph.D. student. In the Lambert lab, a Ph.D. student from Bonn, Andreas Freudenreich, was working next to me as a visiting fellow. I had found out that he was not overly happy about this Ph.D. and that funding after his return was unsecure. Furthermore, I found him nice and original in his thinking, and I had also learnt that he liked adventures. So, I did not think twice and asked him, whether he would like to come with me to build up a lab in Freiburg. He did not think twice either. Thus, in summer 1994, we started in Freiburg. Soon, students appeared from different places of the world and wanted to work with me, although my budget was quite moderate, and I could not offer salaries. My principle was to guide them by inspiration, not by power. It was a great feeling to suggest an idea and see, how somebody else was developing something from that idea.

Just before I finished my time in Strasbourg, I was invited to a Cell Biology conference in Prague to talk about my microirradation story on pattern formation. After my talk, a smiling man with a moustache approached me and asked, whether he could show me something. It was Zdeněk Opatrný, at the Institute of Plant Physiology at the Charles University in Prague. He revealed to me data from a tobacco cell line which he had initiated long back, during the days of the Prague Spring and that had grown as unknown treasure in the shadow of the Iron Curtain. This line underwent a fascinating cycle of cell divisions forming a small file of cells that behaved like a small organism and obviously were "talking to each other". I was tantalised and we started to cooperate, a relationship that is still alive, almost three decades later. He sent students to my lab that helped us to establish the culture, which is still thriving in our lab, although I must admit that I later switched to the more widespread tobacco BY-2 system, because it is easier accessible to molecular biology. We profited a lot from the decades of experience on cell-culture systems of our Prague partners, and tobacco cells have helped us to get insight into the functions of several proteins that connect to microtubules and steer their functions. We also could use them as "minimal organisms" that helped us to understand, how cells, through a self-referring oscillation composed of actin filaments and auxin transport can organise themselves into an organism (reviewed in Nick 2010).

A second line of research addressed the cytoskeleton as a sensory structure. Already in Japan, I had worked on the role of microtubules in gravity sensing, inspired by discussions with Rainer Hertel. I found that, in addition to their role in guiding the growth response, microtubules were needed to perceive the direction of gravity. This sensing was linked with a very dynamic subpopulation of microtubules (Nick et al.

1991). Zdeněk had sent me a young student, Kateřina Schwarzerová (in the meantime she is heading the lab in Prague), to work on the behaviour of microtubules in response to cold stress in winter wheat. While it turned out to be difficult to visualise microtubules in this system, her short stay made me think whether the known cold sensitivity of microtubules might be used by the plant as a kind of thermometer.

But before I could go on, however, I had to work on my habilitation, which forced me to think on the unifying theme of my different projects. I understood that all these projects were dealing with the relationship between cells and the organism they constituted. Whether it was the anthocyanin pattern, where chaotic individual cells responded all-or-none and communicated to generate a smooth and precise readout of the entire organ; whether it was the microtubules that sensed the direction of gravity and translated this into the bending response of the entire organ; or whether a cell activated phytochrome leading to a re-orientation of microtubules which then stopped the growth of the coleoptile, the question behind was always on the relation between the whole and the part. How does it work, if there is no brain, no big boss that rules everybody? Again, I recalled the question from my childhood ("How do they think, even though they do not have a brain"). Writing my habilitation thesis was rewarding for me, although it was sometimes difficult to write it under conditions of a young family—parts of the thesis I had to type with our lively daughter on my lap. Over the years, I had found out that the quest for the "whole" that organises the parts had inspired many great minds from the time of Greek philosophy. My favourites were Ovid, Heinrich v. Kleist and Goethe, and I enjoyed connecting my experiments with their thoughts and concepts, and also paid quite some attention to the rhythm of my language. After six months of writing, I handed in my thesis *Einzelzelle und Pflanzengestalt* (Individual Cell and Plant Shape). I was not overly surprised that the echo in the faculty was controversial. Some found it great, others were furious (the same persons that had already attacked my Ph.D. thesis years before). Again, I was accused of being unscientific because I had mixed science and culture. I was asked to retract and rewrite it in a less provocative way, just giving my papers and some general summary. But I refused because I did not see the point to keep science separate from culture. The scientific method relies on separating observation and interpretation and on a professional way to ask questions, search for answers, fail with these answers and find new, better, questions. But as long as these principles of scientific work are kept, there is no reason, why a scientific text should not also connect to culture. Science is a central part of human culture. So, I decided to fight it through. The following weeks were not overly relaxed, but after all, the majority of the faculty arrived at the conclusion that this thesis was unusual, but of quality. I got my *venia legendi* (the right to teach) and just the next day, my first Ph.D. student defended his thesis under my newly acquired responsibility. After everything was over, the head of the habilitation commission came to me and told me that he had never gone through such a turmoil before, and that he was not even understanding, where all this passion came from. He concluded "You see, science is like a salami, where everybody cuts off only a slice. And you come and take the whole sausage! This is scientific aristocratism!" I answered that his judgement was perfectly right, but that I would stand up for this.

What followed, were two years of extreme uncertainty. The first time in my life I did not live on a fellowship but needed to find short-term contracts, which were difficult to get in the German academic system that basically foresaw only professor positions. Together with other young scientists in a similar situation, I even thought about setting up a start-up (detection of transgenic food), but when we had finished our business plan, it turned out that such a company had just started already, even in our town, Freiburg, and was very successful, since Greenpeace had stopped a boat from the US full of transgenic soybeans, such that the topic attracted a lot of public attention. Twice I was in the situation that I came home Friday evening and did not know, whether it would go on next Monday morning. It always did. The science went fine, my network of colleagues grew, and students wanted to join my team as well, because they had known me as dedicated teacher. I had set up a new type of seminar, where hot topics from widely read papers in high-ranking journals were presented by one student, but where a second student had to play the *advocatus diaboli* and presented a paper that falsified the celebrity (usually these were from solid, but not as high-ranking journals). Then we discussed, what had happened here, and what type of scientific mistake was behind the flaw. Many of my later students came from this seminar, all of them had strong individualities and were somehow "out of the box".

During that time, I also got to know Diego Breviario, who proposed to apply for EU-funding. Twice we failed with two proposals that were scientifically attractive, but obviously did not fit into the policy of the EU system. I became so annoyed by this political component that I wrote up a third proposal, mainly motivated by satirical intentions. It was on microtubules, our common theme, and it drew upon a finding from one of my rice mutants, where a truncated tubulin conferred resistance to microtubule herbicides. We suggested that this could be used as selective marker for transgenic plants—in contrast to the antibiotic resistances used hitherto, it would not be a foreign gene, but a gene that was already present in the plant, just mutated in one base pair (if it were in our days, I would have added that one might engineer this with CRISPR-Cas). With the tongue in my cheek, I thought of a catchy title and called then the whole thing "EcoTub". To my complete surprise, this proposal got funded and so Diego myself and Paul Christou at John Innes started to cooperate. Honestly, this project was not really successful if I look at it from today's perspective. Nature just did not like to have tubulin be messed up (the transgenic cells obviously suffered from the engineered tubulin). However, the project allowed me to extend my group, and I even got a second lab in a new building, where I had additional infrastructure, such as a climatised dark chamber to get my rice to flower. As I had done already in Japan, I needed to transfer the plants from the greenhouse to the chamber—since it was around one km away, I used the bike trailer of our daughter and always caused a lot of ado at the traffic light, when I approached the waiting bikers from behind with my jungle of man-high rice plants in the carriage…

4.9 Never Give Up, at the End Things Will Join

End of the millennium, my career situation stabilised after all—first, I was able to catch an assistant professor position (only temporary, though) and I succeeded to acquire a Junior Research Group by the Volkswagen Foundation. This programme was new and encouraged interdisciplinarity. The new spirit was also manifest in the unusual selection process, where, after a first round of expert reviews, the shortlisted candidates had to convince a jury about the merit of their project. My idea was to look into the dynamics of the cytoskeleton because I had repeatedly encountered the limitation that my microtubule images were just snapshots, but that I could only indirectly infer the processes behind them. I had a quarter of an hour, and in my committee, there was not a single person with a background in biology. I decided to use a metaphor from the theatre world and asked my auditory to imagine someone watching a Shakespearean tragedy in the theatre but falling asleep after the first act and waking up only at the end, when the stage was filled with corpses. This were the way, how a cell biologist feels, when looking on microtubules after stimulating the cell with signals. After my talk, one member of the jury approached me, introduced himself as theatre scientist (I had not even known before that this science existed), and told me "See, I did not understand a word from what you were saying, but I got the spirit that it is significant". I got the grant, which gave me almost 2 million € over five years!

My team grew further and with a pioneering spirit, we explored new fields—for instance, by microinjection of fluorescent tubulin which we purified from calf brain into gravity-stimulated maize seedlings, we could show that the reorientation of microtubules was going through a chaotic stage, where the individual microtubules were either transverse or longitudinal, but where the frequency of those that became longitudinal, increased (Himmelspach et al. 1999). So, even on the level of microtubules, there was an all-or-none decision, as I had seen repeatedly earlier (for instance, in my microbeam irradiation experiments on the anthocyanin pattern). Through the hard work of a Ph.D. student from Tatarstan, Albina Abdrakhamanova, we could show for winter wheat that microtubules, indeed, were thermometers that had to yield in order to induce frost hardiness (Abdrakhamanova et al. 2003). Interestingly, the "hard guys", wheat varieties from Siberia, where those, where microtubules were most sensitive. In the meantime, we have dissected many molecular steps of the underlying mechanism (a recent review is given in Wang et al. 2020) and are currently investigating whether the microtubule thermometer is rather a kind of a clock that measures the timing of a stimulus.

Using the "minimal organism", the tobacco cell line from the Opatrný lab in Prague, a gifted Ph.D. student (actually coming from Diego's group), Prisca Campanoni, discovered that the cell files were all even-numbered, while odd-numbered cell files were rare. Obviously, the cells talked to each other, before they divided. When I discussed this strange phenomenon with a theoretic physicist, Bernd Blasius, at one of the yearly interdisciplinary meetings that were organised by the Volkswagen Foundation for their fellows, he told me that he had been looking for

something like this for years, because he was interested in modelling ecosystems. He asked me for the data, and a few weeks later he came back and told me that he was able to model Prisca's data by assuming that the cells behaved as oscillators that were synchronising their divisions by weak coupling, but that it worked only, when he assumed that the coupling was one-sided—a cell would talk to its right-hand, but not to its left-hand neighbour. While he was rather sceptical that something like that should exist, I asked him to model what would happen, if the weak coupling was interrupted. He did and sent me the data—I asked Prisca to do the experiment, blocking the directional transport of auxin by an inhibitor called 1-Naphthylphthalamic acid (NPA). She did the experiment and found, what our colleague from physics had predicted (Campanoni et al. 2003). In the following years, we could show that actin filaments became bundled, when the cell was depleted from auxin, and that this was inhibiting auxin flow, such that auxin was not exported from the cell, leading to a debundling of actin, which then restored auxin export. This actin-auxin oscillator (Nick 2010) was the base for organising individual cells into a minimal organism. My childhood question for the"somebody" in a plant that is lacking a brain, found an unexpected answer. A plant organism is not a body, an object, but rather a rhythm (for a philosophically stained overview of this research see Nick 2013a, b).

A fourth breakthrough from this time with the Volkswagen Foundation was the discovery that my *hebiba* mutant which I had smuggled in my shoe over the long way with the Transsiberian railway, was not blind at all. It did see red light, and it was endowed with a functional phytochrome photoreceptor. However, the mutant mixed up light and dark. We reckoned that a growth hormone, probably auxin, might be affected in this mutant, and with the group of Elmar Weiler in Bochum that was able to measure the minute amounts of plant hormones in tissues, we investigated the response of different plant hormones to red light. As often, it was an accident that solved the case—our colleagues just set up a new method to measure jasmonic acid, originally discovered as component of jasmin scent, and since our rice samples were still sitting on their bench waiting for being discarded, they decided to check their method on them. Later in the day, I got an excited and exciting call—surprisingly, rice was packed with jasmonic acid, but the *hebiba* mutant was completely void of this hormone (Riemann et al. 2003). Years later, supported by the matchmaker skills of Furuya-*sensei*, my Ph.D. student Michael Riemann succeeded, during his postdoc in Japan, to find the mutation in a gene called Allene-Oxid Cyclase (AOC) that had been hit away by the gamma-rays in the *Gamma-Fierudo* and therefore was not able to provide the precursor of jasmonate (Riemann et al. 2013).

I could have gone on like this for years, but the suspense from unemployment by the grant from the Volkswagen Foundation was limited—five years. I had to find one of the rare professor positions. In Germany, this is not possible in the institution, where you did your Ph.D. One needs to go elsewhere. In 2002, I was participating in more than 10 rounds of "singing" as these events, where shortlisted candidates have to present themselves, are called colloquially. The effort was considerable, but at the end I remained with three options, two of them as an institute director. The decision to go for Karlsruhe, was exclusively based on private grounds—in the meantime, our son had been born and my family did not want to move around in Germany.

Karlsruhe was the only place, where commuting on a daily base would be feasible. So, I picked Karlsruhe. The arrival was sobering—from ten professor chairs, seven were vacant; in rankings on teaching, Karlsruhe biology was on the third position—from the end; the faculty was hierarchic; the institute was romantic, but from the nineteenth century. It was a construction site. I remembered a sentence, which our Latin teacher, a conservative, but just man had taught me, when I was a teenager "*Mallem hic primus esse quam Romae secundus*" (I prefer to be the first here, rather than the second in Rome), said to be uttered by Julius Caesar, while being in a village in Gallia. I was not sure, whether I would be able to compete with Julius Caesar, but I was pretty sure that the place where I had stranded was not Rome. However, I was determined, not to give in, but built up my lab from scratch—fortunately, I had a very good relationship with the people from the workshop of my institute in Freiburg, and they helped me a lot. For instance, they built a custom-made gene gun for me, which costed me only 300 € (and a bottle of red wine) rather than the commercial version, which was more than 20 T€. They revived an antique ultracentrifuge, and also helped me to find second-hand equipment for my new lab. However, it was clear that I needed to force my new university to invest something. Fortunately, soon after arrival, I had been asked to become the Dean of Study Affairs, because, due to the vacancies, all my colleagues already installed before me, were on other duties. Moreover, I had inherited the task to introduce the new Bachelor/Master system. A construction site is also a chance—when everything is crumbled, it is easier to build something new. So, I started to work and reformed the teaching system, against a lot of resistance, but the thought of Julius Caesar helped me to look at this struggle from a larger perspective…

4.10 Whether a Place Will Be a Good Place Depends on What You Make Out of It…

In order to improve my strategic position in addition to having the lead in study reform, I applied for a prestigious institute director position in Salzburg, Austria and was successful. This move helped me to exert pressure on my own university. They had to offer me a leading position and real money to buy good equipment, advanced microscopes in the first place. Most important, they had to offer me a permanent position. After so many years, I could stop worrying about the future of my family and my own existence, which was a great relief.

I will not describe the following fifteen years up to now in the same detail as I did for my early career. It was the time of harvesting the fruits of my former work. I was able to build up a large group, which at peak times counted more than 40 people from many countries, languages, and cultures. I even had to split it into three subgroups, dealing with Cellular Biotechnology, with Plant Stress, and with Applied Biodiversity (I had also become the director of the Botanical Garden).

I will now briefly address three questions that I discovered through these years and that I want to work on in the seven or so years that are left till my retirement:

My old question, how a plant cell can develop directionality and translate this into spatial organisation of the entire organism, had inspired an approach, pursued in my Cellular Biotechnology group, where cells were stripped from any direction by digesting off their cell wall and then let them develop a new direction. Making use of GFP-tagged cytoskeleton marker lines, we could then follow, how the nucleus searched the centre of the cell, while actin filaments and later microtubules organised a new directionality (Zaban et al. 2013). To find out, how individual cells communicate, we needed a new technology. Here, I profited from the interdisciplinary interaction with engineers in my university. We developed a microfluidic chip system that allowed to impose directionality to individual cells by preformed artificial cells (physical stimulus), along with a superimposed chemical cue, a gradient of auxin to see, how the cells will decide about their direction (Zaban et al. 2014). Could we use such chips to mimick the chemical interactions between cells in a tissue? It took a few years, but eventually, we succeeded (Finkbeiner et al. 2022) and could demonstrate that cells in suspension stop dividing, when they feel lonely, but can be induced to enter division, if treated with a conditioned medium from a dense culture. We have already found a molecular candidate for this "social hormone", but we are still not entirely sure, whether we have caught the right fish.

As often, this purely scientific interest led to applications—we could show that secondary metabolites are often produced in a kind of "chemical LEGO", where different cells have to cooperate, and we were able to show the concept by producing the anti-Alzheimer compound nornicotine in cell culture (Rajabi et al. 2017), or by combination of different cell types, the long-desired anti-tumour compound vincristine (Finkbeiner et al. 2022). Could we use this modular principle also for producing valuable compounds from rare and endangered plants? At the moment, we are working on *Cephalotaxus hainanensis*, an almost extinct tree from the Chinese island of Hainan, producing very potent anti-tumour compounds. It is so rare that the trees have to be guarded, because people come at night to steal the bark, which is sold for eight times the price of gold. Based on the transcriptome (Qiao et al. 2014), we work with the team of my former Ph.D. student, Fei Qiao, on reconstructing this pathway by chemical and biotechnological means. This is really tedious work, but we want to demonstrate a new principle and so we just go on drilling. Moreover, our results led me to a new viewpoint—we saw that some of these enzymes localise to mysterious protrusions of the plastids, so-called stromules. Originally discovered by a German cell biologist, Schimper, in the nineteenth century, they were later forgotten and rediscovered in the 1990ies by means of GFP-technology. The original idea of a plastid network that would be physically coupled, could be falsified by elegant experiments with light-switchable forms of GFP directed to the plastids (Schattat et al. 2012). We found out that these stromules can be induced by the stress hormone jasmonate, but also by oxidative stress. They seem to touch other organelles, mainly mitochondria that are oxidatively challenged, and this brotherly tap on the shoulder of their stressed fellows seems to help them to overcome the stress. Thus, the organelles, we know from the textbooks, are apparently much more

interconnected than we think. What we see in the microscope, are just snapshots of dynamic processes, and stromules seem to act on the biochemical and molecular events in a cell. Form rules over Matter? This is one of the questions, I would like to address in the years to come—I am sure, I will not answer it, but the path is more important than the goal.

The *hebiba* mutant that I had smuggled in my shoes was male sterile, but it brought a lot of fruit. We discovered that it coped well with salt stress (Hazman et al. 2015), an emerging problem in many countries like Egypt, Vietnam, or Bangladesh, were the rising sea level makes the soil progressively saline. When we followed this up, we discovered that the stress hormone jasmonic acid, similar to human adrenalin, has two faces—if activated rapidly and degraded rapidly, it is a very important signal that activates adaptation to different stress factors, such as salt or drought. However, if jasmonic acid is produced and stays, this will initiate cell death, and the resources of the dying tissue are mobilised into the young parts of the plant, from where new organs can be reformed, once the stress episode is over. We observed similar phenomena also in grapevine cells and I wondered, how the same signal can mean "life" or "death", just depending on the timing of its birth and decay. In several months of hard work, I developed a model that could explain this phenomenon (Ismail et al. 2014). But how to prove this idea?

In fact, we developed a way, how we could engineer stress signalling with an optimal time course. The details are complex—we used a promoter from a salt-inducible transcription factor, driving a jasmonate-signalling protein where we had cut out a small piece needed for the decay of this protein. The whole cassette was introduced into tobacco cells or real rice plants. Upon salt stress, jasmonic acid was produced due to the salt stress and would have initiated cell death. But since our salt-inducible promoter became active, the jasmonate signalling protein was made and silenced jasmonate signalling, and, because we had cut off the piece needed for its decay, this "off-switcher" remained on all the time. Indeed, the tobacco cells and the rice plants were now able to survive on salty water (Peethambaran et al. 2018).

In the meantime, we found out that also the response to cold stress was depending on temporal patterns. Here, it is microtubules that measure the time and evaluate the stringency of stress and its duration. The outcome is then signalled to the nucleus where different genes are activated that either activate cold hardening, or cold-dependent cell death, such that the resources can be rescued for the younger parts of the plants that will launch a new round of development, once it is getting warm again. To our surprise, this signal is a novel and very exotic microtubule motor, which we baptised Dual Localisation Kinesin. It is running wrong way on the microtubules and when microtubules diassemble in response to cold, this kinesin moves into the nucleus, where it acts as a gene switch and activates Cold Box Factor 4, a master switch for cold hardening (Xu et al. 2018, 2022). Wonders over wonders, which wild imagination could conceive such a crazy mechanism? The older I get, the more often I get astonished.

Salinity, drought, but also untimely cold snaps are events that become accentuated due to global climate change. In parallel, new diseases emerge and spread and challenge agriculture. Over many years and numerous publications, we have dissected,

step by step, the signalling controlling immunity in grapevine. I will not describe the details here, they are very complex, and my brain had to crack really hard nuts to understand this—here, my logical education, which I had obtained as young student in the Schäfer lab in Freiburg, helped me a lot.

I rather want to formulate the question that emerged from this long and complex path. I want to understand, how plants can distinguish the different types of stress. Do they have different signals for each stress? The answer is a clear: no—it is a handful of signalling events, which are used over and over again, jasmonic acid being one of them. However, by combining different signals in a specific temporal order, each stress type leads to a specific signature, which conveys different meanings. In other words: plants use chemical "words", and they combine them in a kind of "grammar". To test this idea experimentally, I asked my former Ph.D. student to challenge rice with different types of osmotic stress where different components were either given separately or in combination (Hazman et al. 2016). The result was intriguing—the plant did not simply add up the response to the components, but each stress combination was processed as a new type of sensory quality—similar to us, when we perceive the combination of blue and yellow as green, even though there is no light of the green part of the spectrum.

In the meantime, we search on the cellular correlates of this holistic property and found out that microtubules are an essential element of "reading" the grammar. I got the honour to be invited to write a review on this idea on behalf of the 50th anniversary of the discovery of microtubules and I took the occasion to develop the idea of a stress grammar (Nick 2013a, b). At some point in the middle of writing, I understood that I am just again asking the question of my childhood "I want to know, how they think, even though they do not have a brain!" The answer is that they use chemical signals just as we use words and that the order of these words in time gives meaning, just as we can generate language by creating rows of words. If I am lucky, I will be able to decipher the "grammar of plant stress", which will allow not only to understand the secret language of plants, but also to make this knowledge useful, in order to render plants more resilient against climate change. Of course, this plan is too ambitious to come true, but it does not matter. According to Camus, one needs to envisage Sysiphos as a happy man…

When I negotiated with the university to ward off the call to take the chair at Salzburg in 2004, one of my conditions was that the university would preserve the Botanical Garden, which was at stake and repeatedly at the brim of being closed down. They agreed, but the deal was that I should demonstrate that the Botanical Garden is relevant to research (under my predecessor, the Botanical Garden was just left alone and was basically a place where plants were grown without any connection with the research at the institute). I thought about a strategy and developed the idea that a Botanical Garden is a place, where plant biodiversity is established and maintained. In a technical university, where engineers dominated, I would need to show that this is useful. Thus, I coined the idea to protect and to valorise biodiversity, focussing on crop plants. Still in my Freiburg time, I had started to cooperate with the State Institute of Viticulture, because they had asked me for support in understanding the cell biology of *Plasmopara viticola*, the pathogen causing Downy Mildew of Grapevine, one of the

most severe diseases in viticulture worldwide. This pathogen is native to the US but was introduced by accident to Europe in the nineteenth century causing tremendous damage and still requiring intense chemical plant protection (around 70% of the total consumption of fungicides in Europe). It was already known that wild grapevines in the US were resistant to the pathogen because they had evolved together.

But what about wild grapes in China? I started to establish a collection of wild grapevines from all over the world, connected to many stories and wild anecdotes, which I will not tell now, because I want to finish the chapter. We found out that some of the wild grapevines from China were resistant as well, but by a different mechanism—they were able to confuse the flagellate zoospores of the pathogen, such that they could not find the entry point into the grapevine leaf, the stomata, and continued to wander around, progressively frustrated, till at some point they tried to develop a mycelium on the surface of the leaf that would die off soon after. We reckoned that the zoospores could sniff out were to go through a chemical signal emitted by the stomata, a kind of mouth odour of the plant. I could convince Prof. Boland at the Max-Planck Institute for Chemical Ecology in Jena to help us finding out, what the signal was. They agreed, and so I drove to Jena with several grapevine plants, a German variety called Müller-Thurgau, and one of the Chines grapevines, called *Vitis jaquemontii*. I still remember, how people stared at me, when I entered the high-speed train with my grapevines that were almost as tall as me. The lab of Prof. Boland had a sophisticated Gas Chromatography/Mass Spectroscopy platform and analysed what the plants were emitting. A few days later we had first candidates for the mouth odour that differed between the German and the Chinese grapevines. We tested those for their ability to attract the zoospores and found out that a small aldehyde, nonanal, was responsible. The Chinese grapes emitted this compound from everywhere, such that it became impossible for the zoospores to find out, where the stomata were. In the process, we also discovered, how the searching worked—as long as the concentration of the attractant was increasing, they were swimming with their flagellae straight, if the concentration was decreasing meaning that they have missed their target, they stretched out the shorter flagellum perpendicular such that the cell was circling around, changing direction, and then trying again to swim straight. In this way, zigzagging, they ended up at the stoma, where they attached and entered the leaf. Actually, these spores are finding their path in the same way as scientists do (remember the start of this chapter).

Soon, the news about our exotic collection spread and I was asked by the Ministry of Agriculture to help them in preserving the almost extinct European Wild Grapevine (*Vitis sylvestris*). A last population grew at the Ketsch peninsula, in an alluvial forest between Karlsruhe and Mannheim. The task was to collect twigs from those grapes, make them regenerate and multiply them for resettlement in the wild in places, where the Rhine had been re-naturalised. To collect these grapes was an adventure because they were growing as lianae in the top of the Ketsch jungle. My technical assistant, Ernst Heene, who was both, a hunter and a native from the Palatinate, a part of German, where the relationship with vine is genetically encoded, caught fire and promised to get all of the wild grapes for our garden. In some cases, he even had to shoot down the twigs from the treetops. The project was successful,

but we were not content in just helping this species to survive, we also started to investigate the immune responses of these plants, as said above, had been working intensively on the signals that regulate grapevine immunity. To our surprise, many of these wild grapevines were able to ward off *Plasmopara viticola*, although they never had any contact with this pathogen from North America. We found out that they were endowed with a strong basal immunity and rapidly accumulated resveratrol and viniferins, defence compounds that kill fungi very efficiently (Duan et al. 2015). For one of our champions, called Hördt 29, we could even find out the reason for this ability—this wild grapevine had evolved a special version of a promoter for a gene switch that turns on the enzymes producing resveratrol (Duan et al. 2016). We demonstrated this, by inserting this promoter sequence in front of luciferase from firefly and shooting this construct into grapevine cells by a gene gun. When these cells were stimulated by signals, the promoter became active and luciferase was made, which we could measure as a light signal with a luminometer. The promoter version from Hördt 29 was much stronger, explaining the better basal immunity.

We understood that our collection of *Vitis sylvestris* was a treasure, full of genes for resilience, which could be used for breeding, because this ancestral species can be easily crossed with domesticated grapevine. Since we knew, which gene variants are relevant, the breeding process can be accelerated, because the offspring of a cross can be checked already at the seedling stage for the desired version of the resilience gene (so-called marker-assisted selection or smart breeding). We have launched this already with Hördt 29, which is resilient not only to various diseases, but also to other stress factors. The news of our collection spread, and I got a request from the Chinese Academy of Science, whether they could sequence the genomes of our wild grapes. First, they wanted the plants, but I refused to give them away. Later, we agreed on a deal—they would get high-quality DNA and we would get access to the genome sequences. In the meantime, we have assembled the entire gene pool for *Vitis sylvestris* that has survived in Germany along with a good part of genotypes from other European countries, and we have established a genome database, such that we can look up for each gene of interest, which variants exist in our collection, go to the garden, pick the leaf, and clone out the respective gene to investigate its function. We have identified resilience factors against many diseases including Grapevine Trunk Diseases that emerge now in consequence of climate change, but also resilience factors against drought, salinity, or heat, problems that will become progressively relevant for agriculture. We want to use this treasure to help breeding new grapevines that can cope with the consequences of climate change.

The grapevine project was something like a paradigm to demonstrate that plant biodiversity is not only relevant for Nature, but also for us, humans. We have added other projects along the same line. For instance, we established a gene bank for Crop Wild Relative which is now part of the Plant Genetic Ressources of the Germany; or we assembled a collection of reference plants for genetic authentication to hunt faked food products, exotic plants that, due to globalisation, enter the European market and are hyped as "super-foods"; or we could show that different Mint species use their scent to kill their competitors by attacking their cytoskeleton (Sarheed et al. 2020). All these projects link scientific curiosity with application (we call this strategy

hypothesis-driven application). “Pure” scientists often tend to look down on applied science—I strongly disapprove this attitude, and I concur with one of the teachings, I had heard from Furuya-*sensei* again and again: “We are all paid by the taxpayer. You should always be able to explain to the taxpayer, what you are doing, and how this, what you are doing, justifies being paid by tax-money.”

The work in the Botanic Garden was thriving, but one day, we received a threat that was existential. A wealthy software company approached the university with the offer to build several huge buildings for informatics, some they would use themselves, others they would rent out, and some would be given to the university. It should be central and close to the Campus. In the eyes of these technocrats, the Botanical Garden appeared as an unbuilt area which was worth a lot of money and was an ideal site. I had to fight a long and sometimes lonely battle against my own university, and if I had not demonstrated before that the biodiversity established in the Botanical Garden is of value also for the taxpayer, I would have lost the battle. Even so, it took many years, and I felt like David against Goliath. I did not use a sling, but I had to employ the entire repertory of tricks which I had been taught by Furuya-*sensei*, also activating my entire political network to resist. Eventually, they promised a new garden at a site nearby with new greenhouses and even a new institute building. The budget, which is considerable, has just been approved by the parliament end 2021 and I hope to see the new garden before I retire. This investment would then also secure the existence of the Botanical Garden after my retirement, it is the only material legacy, I want to leave behind (otherwise, I consider only the legacy from our actions and inspirations as real, but here I make an exception).

4.10.1 Don’t Be Afraid from Taking the Lead—It Is All About Communication in the First Place

I want to conclude this chapter with some remarks about leadership, because scientists often forget that their path will lead them one day into a position, where they have to lead others, and to my opinion, they are rarely prepared for this. The conventional model for leadership is that of a hierarchy, often accompanied by psychological pressure. As I know from my own career, young scientists are extremely vulnerable and dependent on the benevolence of their bosses. To push them to work even harder, seems an easy job, since their perspective is unsecure over many years. However, I strongly despise this approach—it is immoral, it is exploiting, and it is not sustainable. Science is rooted in strong personalities. Personal motivation is the most important driving force (and the only driving force that matters to my opinion).

Thus, I did not even try to lead such a big group by hierarchy. Instead, I tried to learn from the way, how plant cells organise themselves into an organism. They do this by communicating with each other all the time and by synchronising their individual rhythms. Following this principle, I mainly worked on rhythmic communication, which means that I have frequent meetings with all three subgroups, but also with the gardeners, the technical staff, and of course, with the entire institute. While I leave a lot of individuality to everyone, also with respect to working time, I insist

that everyone participates in these meetings, and when somebody does not show up, I do ask for the reason. My friend, Diego Breviario, had introduced to me, some years ago, the work of John Mattick, who wrote an inspiring article about the role of non-coding sequences in evolution (Mattick and Gagen 2001). He pointed out that it is not the number of genes that determines the complexity of an organism, but the number of their interactions. If the number of nodes in a system grows by a factor of n, the number of interactions needs to grow by the n^2. I took this very seriously in my group and worked mainly on the structure of interactions and on clear communication channels. The second duty I have is to inspire my people, to help them in finding the story in their data and to support their scientific and personal development by discussion and advice. One lesson, I have learnt from Furuya-*sensei* is, that as a leader, I always need to respond, if somebody asks me, and if I have no time now to deal with the matter, I need to give at least this reply. He taught me that the more one advances into a leading position, the more obliged one should be to communicate and respond to everyone—the only power that is real is the virtue of communication. Of course, I am not naïve and know that this virtue is often ignored, but a moral value remains in effect even if it is ignored by many.

I enjoy helping young people from all over the world to develop on their path. I also enjoy teaching young people and watching them, how they find questions and answers, and I greatly enjoy the freedom to shape my work following my interests, to develop ideas, and make them tested experimentally. Of course, there are also less pleasant aspects of my work, such as hunting for the money to run my lab or sitting in endless committees. Of course, I also have to act on the political level, which is not the thing, what really interests me. However, I also have learnt to use power, if it is necessary, but the cases, where I have to rely to this means, are rare, and if this happens, it is directed against the bureaucracy or the leaders of my university, not against those that depend on me. In the times, when I suffer from this aspect of scientific life, I recall Furuya-*sensei*'s lessons, who not only taught me many tricks, but also a perspective on science as a common endeavour of humanity that we get as legacy from our teachers and that we have to pass on in good shape as legacy to our students. This perspective helps me to live through the less pleasant aspects of being the head of a chair at university. Overall, I cannot imagine any other work that would give me that degree of fulfilment.

5 Advice to the Next Generation of Scientists

BELIEVE IN YOUR QUESTIONS! The previous section was quite detailed, and this had a reason. All these examples, highlighting my scientific path, tried also to illustrate some general points or advice that I want to pass on to the next generation. In the final section, which will be much shorter, I try to formulate those points explicitly. In this explicit form, these statements may appear a bit abstract, but this is intentional. To render an advice fruitful, you need to translate it for the own path. Each path is different and individual (this is already the first statement).

5.1 Try to Stay Rooted

If you are looking for a predictable, stable, and regular life, it is probably not a good idea to become a scientist. As you can see from this chapter, moving around in the world as well as coping with unsecure perspectives are typical elements of a scientific career. It is important that you balance this in your personal live. Only then will you have the energy to stand the volatility of scientific life. Your cultural background, important habits that come with your upbringing (for instance, food or music), a close relation with loyal friends, or following a non-scientific passion will help you to withstand the unsecurity and challenges arising from living as a scientist. It is inevitable that you also will move through times of conflicting demands—for instance, when you have small children, it is not possible to work late hours or to visit a conference, even if your boss would like you to. One needs to find compromises. This does not mean at all that you are a bad or non-dedicated scientist. It just means that, as a human, you are more than just a scientist. When you have to make important decisions, always hear what your beloved ones think about it. If they think that this move may be good for your career, but bad for them, you have to take this seriously, and if the move would disrupt your family or relation, decline it.

5.2 Search Mentors that Do Not Instrumentalise You

Especially during the early part of your career, you rely on mentors, which brings you into a state of dependency. Their benevolence and support are not only needed to help you through the formal steps of your scientific curriculum. If you do not have your own funding, for instance, through a scholarship, you may need a working contract from them. After you have defended your Ph.D., you will need them for reference letters that open doors to other opportunities. Last, but not least, biology is an experimental science, and to be competitive, you need a certain infrastructure and funding for your experiments to proceed. Your mentors, on the other hand, are also subject to competition for funding and sometimes also for their standing in science, especially, when they are driven by personal ambitions to climb up the hierarchy of scientific and political power. To find the right mentor is pivotal, therefore. Some mentors consider their students as tools to support their own path, rather than as young scientists that strive to develop their own scientific profile. Of course, it is difficult to predict, how it will turn out to work in a given group, but you should keep your eyes and ears open, before you accept an offer to join a given lab. What type of paper does the lab publish—do you see that each Ph.D. student comes up with his or her story, or are these papers with numerous authors, possibly published in high-ranking journals, but with many former lab students sandwiched in a long list of authors, and just the one, who was happy enough to join the lab, when the story was ready to be completed in the life time of a Ph.D. student, had the profit in form of a first-authorship position? How is the mentor talking about his people? Do you have the feeling that there is an

atmosphere of respect and cooperativity in the lab, or are the students all working separated, possibly even against each other? Are there regular group meetings, are the discussions there open and supportive, or is there an air of fear and mistrust? Most importantly: do you feel that the mentor is a happy person with a generous and supportive character? What are the motivations behind the research of the group—are they mainly thinking about money and reputation, or are they genuinely interested in understanding Nature's mysteries, are they interested in using science to make our world a better place? If you feel that some of these questions would be answered by "no", you should look for a different mentor, because there is nothing worse for young scientists than a mentor that tries to use them as instruments to boost the own ego.

5.3 Follow Your Gut Feeling

The path of a scientist is a path through a jungle. Whether your path will lead you somewhere, you can never tell. Actually, nobody can tell. You need to pass uncharted territory, often under unclear or even unsecure circumstances. The temptation to get hold of anything that appears stable is strong, therefore. To refuse an opportunity that is offered to you may appear like acting insane. However, don't let yourself be overwhelmed, but ask for a short time to think and then listen to your guts. Do you feel comfortable in presence of the person who offers you the job or place in the lab? Or do you perceive some kind of uneasiness? If so, follow your gut feeling and not your neocortex that will provide you with numerous rational reasons, why you should accept the offer (although the same neocortex is as readily able to provide you with numerous rational reasons, why you should not). Decisions are often depicted as branching points that will decide your future path (I have to admit that I also did this repeatedly during this chapter). This may not be totally true. It is not the decision, but what you make out of it, what really matters. Why should the paths through the jungle only split up? They might as well merge at a later point—I have experienced this several times. In order to develop out of a decision something which is fruitful, the circumstances along the path are more relevant than the question, whether you had turned to the left or to the right in the beginning. Such a decision is usually a multifactorial situation, which very quickly goes beyond that what we can grasp rationally. Your gut feeling acts in a holistic manner, it may perceive the unspoken signals of a person, promising you a pink future, it may notice that the facial expression of the person does not entirely match with the content of the words. The discrepancy may be subtle, and your consciousness may not pick it up, your gut feeling will. It is rarely scientific content that decides about success or failure, but the atmosphere in your lab, the support by the others, the spirit of inspiration that provides you the energy to go on and overcome the many difficulties and frustrations that usually line the path of a scientist. If the atmosphere is bad, it will suck the spirit

out of you, and you remain like a zombie, filled with fatigue and depression, which will make you fail inevitably. Your gut feeling can protect you from that. Take it seriously.

5.4 Ambition is Fine, But It Should Not Be Personal

As I tried to convey to you in this chapter, science is motivated by questions, sometimes by bold questions. To follow this up, requires a certain degree of megalomania, and this is perfectly fine. Because it is clear that you will need to pass not only through periods of hard labour, but also of frustration, and your vision needs to carry you through all that, often over many years. However, this ambition should be directed on your idea, not on your person. Whether it is you or somebody else, who discovered something is actually irrelevant. Did you know that the half-time of biological knowledge is around five years? In five years from now, half of the knowledge has become irrelevant, in ten years, only a quarter is still valid. So, even the most prestigious breakthrough will become inevitably annihilated by the course of time. What your name is in science, matters only for a few years, what matters more, is the impulse you gave to science, it will survive you, inspire those coming after you and bear fruits that are quite different from those you anticipated.

5.5 Do It Your Way

Doing science successfully, requires a long training and a lot of skills. If you do not apply a method appropriately, you will simply fail to get results. One needs to respect the rules of handicraft to become a good artist. However, there is a level beyond methodology, and, here, it is important that you follow your question, and not the question of somebody else. If you find something new, it is rarely easily understood or adopted by the majority. Usually, you will encounter scepticism and sometimes even resistance. Don't yield too easily—if somebody gives you a good ground that your idea is wrong, then you have to yield, but only then.

5.6 Have Fun

Knowledge does not fall from sky, it has to be searched, often through blood and sweat. One needs a certain degree of stoicism to go through all that, but one can only do so, if one is able to feel the bliss of finding out a secret, to make connections between parts that seemed unrelated before and now begin to make sense. So, do not forget to have fun in doing science, cherish the moments, where something which you

predicted became manifest in the experiment you conducted to test your prediction. This is not only perfectly alright, but it also keeps us going.

5.7 Trust and Be Trustworthy

Scientists are individuals, but they are never alone. Your question crystallised from the work of others that have asked other questions, and your answer will inspire those that come after you. This vertical line is accompanied by a horizontal plane—at the same time as you follow your questions, others follow theirs and those that support each other will advance. Cooperation will also help you to integrate different viewpoints on your matter. Never forget that observation is never objective, nor is experimentation. Both have a purpose, coming from the reasoning you invested before setting up the experiment. During this reasoning, you had to reduce the complexity of reality to some aspects, which you can and want to address in your work. Perhaps you have chopped off an important aspect that you will not see then. Your colleague, who looks at the phenomenon from a different angle, my see, what you don't. Thus, cooperation is the core of science, and it must never be sacrificed to competition. Cooperation is based on mutual trust. Search people, whom you trust, and be trustworthy for others. Only then will you be able to become a good scientist.

5.8 Be a Citizen of the World

Science is and has always been crossing borders of language, culture, and geography. It is amazing to see, for instance, how during the early Middle Ages, when Christians and Muslims were caught in everlasting warfare, scientists from both sides exchanged ideas, concepts, and methods. While science always requires personalities, it is and should be independent of collective constraints. Whether the scientist, who proposed a theory, is from Patagonia, or from Germany, is completely irrelevant, as well as if this person is male or female or something else, relevant is only the content of the theory proposed by this person. You can also turn this argument: If science is independent of all separations that are artificially constructed by humans, it is also overarching all humans, beyond these separating categories. Scientists are, thus, members of a community that follows a common set of virtues:

- *Justitia.* To be successful, they need to seek for fairness—since nobody of us knows the truth, we always have to weigh the arguments in favour and against a theory, even if it has been developed by ourselves. If we neglect fairness, we will, sooner or later, run astray in the jungle of the unknown.
- *Veritas.* As scientists, we know that we will never be able to see the world as it really is. At best, we will move in our work towards something like scientific truth. The only thing, we can do, is to be authentic, work, think, and speak carefully,

avoid mistakes to the best of our knowledge and correct them, when our knowledge has grown far enough to see that we went astray.

- *Temperantia.* To go on our path, which is often not an easy path, we need enthusiasm and inspiration. When, after a long struggle, we succeeded to extract a piece of consistent reality from the fog that surrounds us, we feel a bliss, because we have created an image of the world that fits together and allows us to see a part of the beauty of Nature. This bliss comes with a risk, though. We can get drunk from it and easily overstretch the image we have created. Like Narziss, who fell in love with his own mirror image, we stop then to continue our path. Especially in such moments, it is important to pour some modesty into our temporary victory considering that our image has been created by reducing the complexity of reality to some aspects we can grip and humbly acknowledging that even the most powerful theory is only an approximation to a far more complex reality.
- *Fortitudo.* To search a path in the fog means, one has to walk, where nobody else has walked before, leaving footsteps on virgin ground. Whether this path will lead somewhere, or whether it is a dead end, we cannot know before we have walked it. This needs courage. Without courage, there is no science. Even when our path has been successful and we arrived on a hilltop that allowed us to oversee part of the landscape, it will need even more courage to tell this to others that have not been there and first are reluctant to follow.

So far, a translation of Aristoteles Cardinal Virtues into the world of science. Whoever follows these virtues as part of scientific professionality, will also need to live those virtues as a person, because personal authenticity is a precondition for the professional use of these virtues. In other words, the professional virtues of scientific work establish a framework that can be used, when people from different backgrounds encounter. Scientists are citizens of the world. Citizenship has some consequences—a citizen is a free member of a city, but on the other hand, a citizen bears responsibility for the city. Science can only thrive in an atmosphere of freedom, freedom is not a gift from the Gods, it has to be achieved and cultivated by everybody of us, every day.

5.9 Cultivate the Art of not Knowing.

Science is not a religion, and it does not enshrine a "truth" whatsoever. It is more something like a scouting art—while we are searching for our path in a forest, nobody of us has the privilege to fly like an eagle over the landscape and see, where these paths are leading to. We can only pursue our own path as long as it appears successful to us, when we get stuck, we have to change direction. Whether the new direction is better than the former, we will only find out by walking. As long as it is clear to us that we are not in the position of the eagle, but in the position of those walking in the forest, all is fine. But this is not enough. We should not be angry about the infinity of this forest, which will never be grasped by our minds. In the opposite, we should

be happy about this infinity, because it will keep our fascination alive, our fire burn, and our steps move on. It is the process of walking that matters, not the path that we have achieved.

So, just go ahead!

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